STUDIES ON THE FLUIDISED BED GRANULATION PROCESS

by

Michael Banks, B.Sc.(Hons.) Pharm.

Thesis Presented to the Council for National Academic Awards for the DEGREE OF DOCTOR OF PHILOSOPHY.

School of Pharmacy,
Leicester Polytechnic,
Leicester.

in collaboration with

Riker Laboratories,
Loughborough.

Submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy.

June, 1981

ACKNOWLEDGEMENTS

I would like to thank most sincerely all my friends and colleagues who have contributed to the completion of this thesis. In particular I would like to acknowledge the individual participation and encouragement of the following people:

Dr. Michael E. Aulton, as internal supervisor for his contribution to the guidance and planning of the project and constant encouragement.

For stimulating discussion: Mr. W. Kirk (Riker Laboratories) and Dr. S. Proudfoot (Leicester School of Pharmacy).

For technical assistance: Mr. R. Rue and Mr. H. Cragg (Leicester Polytechnic).
Mr. D.K. Smith of Riker Laboratories for use of the instrumented tablet machine.
Mr. M. Wedd and Mr. P. Faraday (Malvern Instruments) and Dr. P. Felton (Sheffield University) for use of the Malvern ST 1800 droplet size analyser.

The management of Abbott Laboratories, International Division for providing the opportunity to complete this thesis.

For photographic services: Mr. A.J. Page, A.R.P.S.

For typing services, often under extreme pressure of work:
Mrs. S. Illsley and Mrs. J. Wallace.

Finally my parents and fiancee for their patience and support.

CONTENTS

STUDIES ON THE FLUIDISED BED GRANULATION PROCESS

by

MICHAEL BANKS

ABSTRACT

This study is an evaluation of the process of fluidised bed granulation with the objectives of elucidating the mechanism of granule formation and identifying the fundamental parameters affecting granule quality thereby enabling the true benefits of the process to be realised.

Initially the effect of seven process variables upon granule quality was quantified using a factorially designed experiment. During granule assessment the torque generated by a paddle revolving in a granule mass was shown to be a useful measure of granule quality. The variables found to exert a significant effect upon granule quality were those which affected the wetting of the powder mix and rate of evaporation during granulation. A closer examination of those factors influencing bed wettability was indicated. This was achieved by studying the spray characteristics and droplet size of the atomised granulating solution, and investigating powder bed hydrophobicity.

Spray characteristics of the atomised granulating solution were measured using a Malvern ST 1800 Particle and Droplet Size Analyser. A direct correlation was shown between droplet size and granule size. Coarse, free flowing granules were obtained from sprays with large droplets, wide droplet size distributions and high granulating solution addition rates.

A linear relationship was shown between the cosine of the solid/liquid contact angle and granule size. The addition of surfactant (sodium lauryl sulphate) to a model hydrophobic system was shown to improve granulation. This was related to improved powder/liquid affinity. Surfactant dissolved in the granulating solution gave slightly coarser granules with improved flow properties than when added directly to the powder mix. This was attributed to changes in spray characteristics and improved wetting by the atomised granulating solution.

The growth mechanism and granule structure were subsequently investigated in a number of model powder systems using sieve analysis, scanning electron microscopy, a specially developed fluorescent technique to monitor binder distribution and a solvent extraction procedure which left a network of binder. Close examination of the data enabled a growth mechanism to be proposed for lactose and modifications to this were discussed for the other materials investigated.

Thus, based on the changes occurring in the microenvironment during powder particle/droplet collision, those factors which significantly influence granule formation have been identified. These were principally the physico-chemical properties of the starting materials and the properties of the granulating droplets.

List of Figures

List of Tables

CHAPTER 1

INTRODUCTION AND SCOPE OF THESIS

1.1 INTRODUCTION

1.2 GRANULATION

1.2.1 Precompression

1.2.2 Wet Granulation

1.2.3 Theoretical Aspects of Granulation

1.2.3a Bonding Mechanism

1.2.3b Mechanism of Granule Formation

1.3 FLUIDISATION

1.3.1 Fundamental Concepts of Fluidisation

1.3.2 States of Fluidisation

1.4 FLUIDISED BED GRANULATION

1.4.1 Fluidised Bed Granulator Design

1.4.2 Fluidised Bed Granulation: A Chronology

1.4.3 Discussion of Fluidised Bed Granulation

1.4.3a Product Parameters

1.4.3b Process Parameters

1.4.3c Apparatus Parameters

1.4.3d Safety

1.5 SCOPE OF THESIS

CHAPTER ONE

INTRODUCTION AND SCOPE OF THESIS

1.1 INTRODUCTION

Over the past two decades extensive work has been carried out in pharmaceutical process development to improve and quantify the granulating operation. The benefits of these studies include reduced processing times (with associated lower costs) and improved physical characteristics of the resulting granules (such as flow and compaction properties), with the long term aim of manufacturing tablet granules from which tablets with reproducible bioavailability can be produced.

During the early 1960's four major new techniques were described for tablet granulation:

(i) A one stage operation in a modified rotary vacuum dryer with the mixing of low potency formulations being demonstrated (Cooper, Swartz and Suydam, 1961; Goodhart, Draper and Ninger, 1970).

(ii) Spray drying (Raff, Robinson and Svedres, 1961) of slurries containing active ingredients and tablet excipients to form free flowing granules of uniform distribution. Advantages of this technique include the elimination of dye migration thus preventing possible tablet mottling.

(iii) Granulation in pans (Tuerck, Walters and Carkhuff, 1960 a and b; Ahmad and Pilpel, 1967) in which a powdered formulation is sprayed intermittently with granulating solution until granule formation is achieved. The process then continues with tumble drying.

(iv) Granulation within a fluidised bed by spraying a binding solution onto fluidised powders. This was first demonstrated by Wurster (1959, 1960) in a small laboratory research apparatus.

At present the most widely used of the above four methods is fluidised bed granulation (FBG). Although Wurster published his work in 1959 it has not been until the 1970's that any widespread pharmaceutical

interest has been shown in the process. A large number of pharmaceutical companies in the late 1960's purchased FBGs as being the granulator of the seventies (Wørts, 1972) since all the multistage operations of conventional wet granulation could be performed in this single piece of equipment thus eliminating costly labour charges. However, a large number of existing formulations could not be easily transferred without lengthy, expensive redevelopment work. This sometimes necessitated reformulation which resulted in further problems associated with registration health authorities. During this period a new breed of impeller mixers with high speed cutters emerged which offered quick, reproducible granulation without having any significant formulation dependency. Thus the pharmaceutical industry steered towards this technology and interest in the FBG diminished. Many FBGs were relegated to a drying function only.

It is suggested that the change in emphasis from FBG technology to the faster high speed mixers was rather premature since the real benefits of fluidised granulation had not been exploited. The reason for this is considered to be the initial lack of research into the fundamental, underlying mechanisms of the process. It is the aim of this study to attempt to identify and where possible quantify these mechanisms.

1.2 Granulation

Granulation has been broadly used to describe several unrelated processes or operations whereby material in powder or solution is converted into granules. The process is primarily one of size enlargement and has been defined in Perry's Chemical Engineer's Handbook (1973) as 'any process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified'. Such processes or operations include spray drying, rolling, extrusion and pressing. Granulation is not considered as being a unit operation itself but utilises certain unit chemical engineering operations (Newitt and Conway-Jones, 1958).

Within the pharmaceutical industry granulation is generally regarded as being the conversion of powders into agglomerates which have physical properties not possessed by the original material. The granules produced offer many advantages in tablet technology since they help overcome the following problems associated with fine particle

Segregation: granules can give improved content uniformity of active drug or excipients present in small quantities.

Flow: granules give improved flow properties which are necessary for high speed rotary tableting machines. More uniform feed rates reduce tablet weight variation.

Dust: granules may reduce the problem of cross-contamination and machine malfunction thus adhering to Good Manufacturing Practice.

Compression: granules have superior pack down properties than powders and this results in more uniform die fill and therefore tablet weight variation. Granules more readily transmit compression forces and bond to form stronger tablets and more uniform distribution of pressure.

The manufacture of granules helps overcome the problems identified above and thus enables tablets to be produced having reproducible physical properties with good weight and content uniformity.

Pharmaceutical granules have normally been provided by two methods:

1.2.1 Precompression

This process has been used for many years and is achieved by slugging which essentially consists of preparing large (30 - 50 mm diameter) tablets from a dry, highly lubricated powder blend on a heavy duty press then chopping up the slugs, relubricating and recompressing (Peck, 1939). The process is however very time consuming and the added compression step necessitates the use of large amounts of lubricants which may adversely affect biological availability. This method is generally only used when one or more of the formulation ingredients are either unstable in polar solvents or are thermolabile.

1.2.2 Wet Granulation

This is a multistage process consisting of blending, massing, wet screening, drying, dry screening and lubricating. It is the most

widely used method of granule preparation in the pharmaceutical industry. The starting materials are usually of the same approximate particle size to alleviate any problems of blend uniformity during mixing. Granule formation is by sticking the powder together with a binding agent to produce the required adhesion. Common binders are starch mucilage, polyvinylpyrrolidone, gelatin and methylcellulose. These may be included in the initial powder blend or more commonly dissolved or suspended in the solvent and added to the powder mix as a solution or slurry. The amount of solvent and the subsequent degree of mixing is critical since the mass should be moist but not over-wetted. Once the binding solution is added mixing continues until a uniform mass is attained. The kneading for the shear required during mixing is supplied by vertical shaft, sigma bladed or horizontal shafted mixers.

After fluid addition the mass is wet screened; this breaks up the wet mass into coarse aggregates. This material is dried and the resulting granules passed through a fine screen to remove any oversize material, lubricated and then compressed into tablets.

The wet granulation method as described above is an extremely labour intensive operation and utilises several pieces of expensive plant machinery. Various attempts at quantifying the procedure by optimising the individual stages have resulted in reduced costs. This has been specifically evident during the drying stage which was traditionally achieved by large tray ovens. The introduction of fluidised bed technology however had an extreme influence upon this hitherto rate determining step since lengthy drying times of several hours were reduced to minutes.

Direct compression bases are also used to prepare tablets. This method of tablet manufacture principally rests on the use of an inert, free flowing, easily compressible material which can be directly blended with the active drug and other formulation excipients.

1.2.3 Theoretical Aspects of Granulation

Scientific studies on the process of granulation began only about 20 years ago. Research into the theory of granulation has shown that it can be affected by the type of granulator used. Most of the work has been performed in pans and drums in the particle size ranges slightly greater than those used in pharmaceutical tabletting. Because of insufficient fundamental and operational research many of the different types of granulators available are based upon an empirical foundation. There are however certain mechanisms which are independent of the granulation method; these can be classified into two categories.

1.2.3a Bonding Mechanisms and growth mechanisms

Rumpf in 1958 classified the bonding mechanisms acting between small particles into five major groups (Table 1.1). It is perhaps worth describing these groups in view of the later work reported in this thesis. Those mechanisms which are of particular relevance to pharmaceutical systems will be identified.

Table 1.1. Rumpf (1958) Classification of Fundamental Bonding Mechanisms

A.	Solid Bridges.
B.	Boundary surface forces and capillary pressure at freely moving liquid surfaces.
C.	Adhesion and Cohesion forces in agglomerate bridges not in motion.
D.	Attraction Forces between solids
E.	Interlocking bonds.

A. Solid Bridges

This section can be further subdivided into five categories of which only two are common in the binding mechanisms of pharmaceutical granules during drying and after wet granulation.

(i) Hardening Binders

The most common hardening binders in pharmaceutical granulation are gelatin, polyvinylpyrrolidone, starch mucilage and carboxymethylcellulose which form solid bridges between particles during drying. Pietsch (1965) and Pietsch and Rumpf (1966) derived an equation for the tensile strength of an agglomerate with solid bridges.

(ii) Crystallisation of dissolved substances

During drying of granular substances any dissolved material in the granulating liquid crystallises out forming crystalline solid bridges between the interparticulate contact points. The strength of the crystalline bridge depends upon:

(a) the amount of substance deposited.

(b) the crystallisation rate which also affects the size of the crystal which may, in turn, influence the rate of dissolution.

(c) whether the dissolved substance crystallises in the early stages of drying on the surface of the wet granules and forms a crust. This also has a predominant influence upon drying rate.

The other three mechanisms classified under the heading of solid bridges are, in pharmaceutical applications, only known in exceptional circumstances ie. sintering, chemical reactions and melting adhesion.

B. Boundary surface forces and capillary pressure at freely moving liquid surfaces (capillary adhesion forces).

Liquid bridges are the pre-requisite for the formation of solid bridges (hardening binders) and are the most important binding mechanism in wet granulation. Addition of liquid to material initially produces bonds of increasing tensile strength as higher proportions of liquid are added. There are three, classic, states of water content which can be distinguished in granule formation, as shown by Newitt and Conway-Jones (1958).

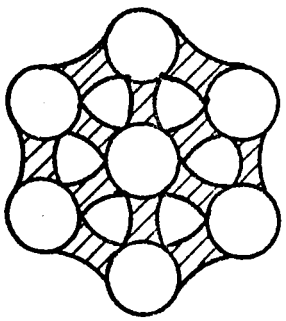
With low moisture contents water is held in the granules as discrete lens shaped rings at points of contact of the particles. This is shown in Fig 1.1.1 and is termed the PENDULAR STATE. In this case two forces contribute to the tensile strength of the bonds:

(i) the surface tension at the concave liquid-air interface of the bridge.

(ii) the hydrostatic suction pressure in the bridge.

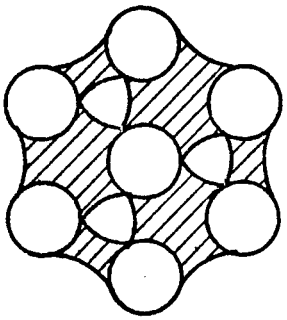
At higher moisture content levels the rings coalesce and a continuous network of liquid interspersed with air is obtained. This state is termed FUNICULAR (Fig. 1.1.2) with Rumpf (1958) deriving an expression for its tensile strength.

Fig. 1.1 Binding mechanisms by liquid bridges.



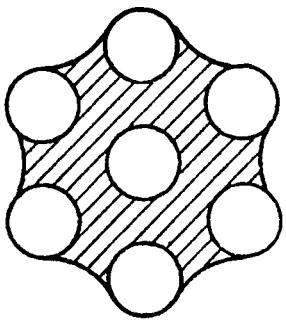
PENDULAR

Fig. 1.1.1



FUNICULAR

Fig. 1.1.2



CAPILLARY

Fig. 1.1.3

When the void space is completely filled with liquid Fig. 1.1.3, the granule is held together by capillary suction at the concave liquid/ air interface on the granule surface. Surface tension at the air/liquid interface also affects the strength although it has been shown by Rumpf to be negligible when compared to capillary pressure. This is the CAPILLARY STATE (Fig. 1.1.3).

Tensile strength of a granule as a whole is approximately equal to the average capillary pressure $\bar{P}$ where:

$$\bar{P} = \frac{T}{M} \cos \theta$$

T = Surface tension of liquid

θ = Solid-liquid contact angle

M = The mean hydraulic radius of the pores

C. Adhesional and Cohesional Forces in immobile bridges

There are two possible bonding mechanisms which can be classified in this section.

(a) Viscous Binders

When thin layers of viscous binders, adhering to the solid, are introduced between the particles, the effect of the interfacial forces upon the shape of the liquid surface is reduced. The reduced mobility results in the bond strength being orders of magnitude greater than that in freely movable liquid bridges (Rumpf, 1961). Many binders harden after a certain time and form solid bridges.

(b) Adsorption Layers

Rumpf (1961) stated that thin adsorption layers were also not freely movable. Aqueous adsorption layers of less than 3nm transmit the forces of molecular attraction between particles if they are in contact. This normally only occurs at the peaks of roughness (asperities). Under high pressure the areas where adsorption layers are in contact can be greatly increased thus giving rise to high bonding forces.

D. Attraction Forces between solid particles

This section is subdivided into three categories with the forces existing without the aid of material bridges.

(a) Molecular Forces — These are short range Van der Waals forces and form interparticle bonds mainly between fine particles.

(b) Electrostatic Forces — Electrostatic charges contribute very little to the final strength of the granule although they may play an important role during the initial formation of agglomerates.

(c) Magnetic Forces — These have no relevance to pharmaceutical powders.

E. Interlocking Bonds

Fibrous lamellar and bulky particles are likely to interlock or fold about each other thereby forming closed bonds between particles. This bonding is rare in the formation of pharmaceutical granules.

1.2.3b Mechanism of Granule Formation and Growth

The process of wet granulation in pans and drums has received much attention and the mechanisms can be divided into three stages (Barlow, 1968) and these are displayed in Fig 1.2.

(i) Nucleation Stage

Loose agglomerates and particles are initially wetted by the binding solution and form small granules by pendular bridges (Fig. 1.1.1). With increased addition of binder solution and the tumbling action within the pans and drums, nuclei form with capillary forces holding them together (Fig. 1.1.3).

(ii) Transition Stage

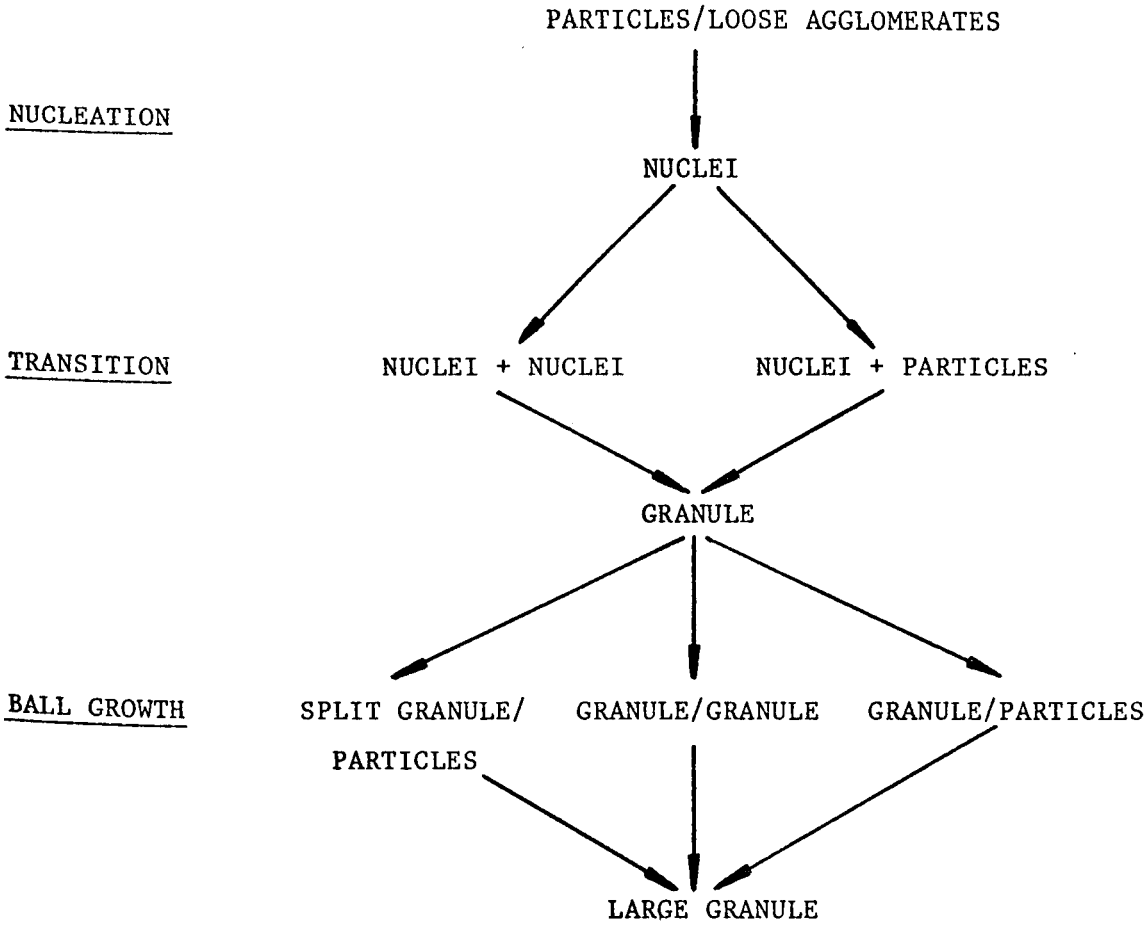
In this stage granule growth can occur by two possible mechanisms:

(a) Single particle addition to the nuclei by pendular bridges.

(b) Combination of two or more nuclei followed by reshaping due to the tumbling action within the granulator.

Thus there is a large number of small granules with a fairly wide size distribution at the end of this stage.

Fig 1.2. Three stages of granule Formation and Growth Mechanism.



(iii) Ball Growth

Ball growth is the stage when large spherical granules are formed. With respect to pharmaceutical granulation this is an advanced stage of growth and is therefore never aimed for. Much research has however been performed in this growth area resulting in three mechanisms being postulated (Fig. 1.2).

(a) Newitt and Conway-Jones (1958) postulated that further growth took place by the larger granules breaking into two or three pieces which subsequently recombined with small particles to form a much larger granule.

(b) Kapur and Fuerstenau (1966) suggested that large granules were formed by coalescence of two or more granules regardless of their relative size.

(c) Using different coloured sands, Capes and Danckwerts (1965) demonstrated that selected comminution of the smaller granules occurred. The resultant particles were then distributed over the surface of the larger granules. The introduction of dyes into their system has been questioned (Sastry and Fuerstenau, 1973) since they may affect the wettability of particulates with possible changes in growth behaviour.

Work by Sastry and Fuerstenau (1973), using calcites with similar pelletising behaviour but different fluorescencecharacteristics has shown that the mechanism of ball growth is in fact a multistage process. These stages being defined as coalescence (Kapur and Fuerstenau, 1966), breakage (Capes and Danckwerts, 1965) and abrasion transfer. The term abrasion transfer describes the mechanism whereby a certain mass of material is transferred from one species to another due to interaction and abrasion of the agglomerate species. It is a mass transfer process whereby there is a continuous change in size of agglomerates without changing the total number of agglomerates.

The Newitt and Conway-Jones (1958) postulation has been all but discounted since it has been shown that large granules break into many daughter fragments either all of the same size or of different sizes (Sastry and Fuerstenau, 1973). These fragments then redistribute onto surviving granules thereby causing layering (Capes and Danckwerts, 1965).

1.3 FLUIDISATION

Fluidisation technology has been known for many years and is widely used in the chemical industry (Sittig, 1953; Priestly, 1962; Leva, 1959). It has however only been applied to the manufacture of pharmaceutical products over the last twenty years. Applications in pharmacy include drying (Scott et al, 1963; Quinn, 1963; Vanacek,

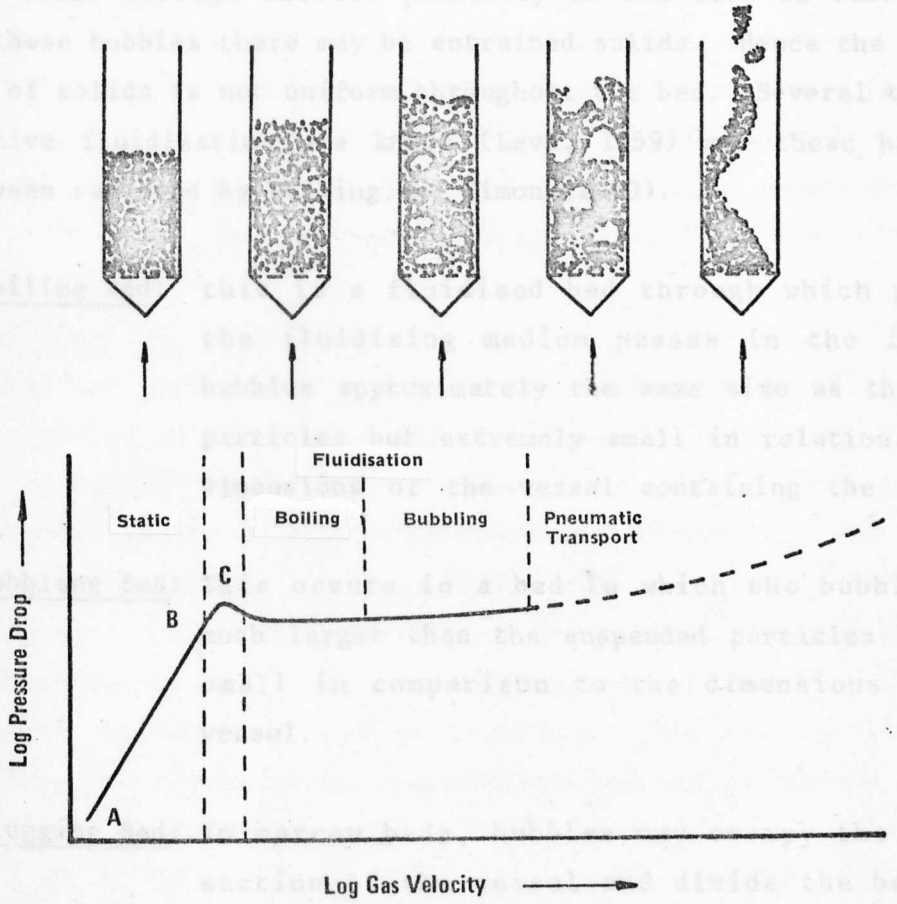
Markvart and Drbohlav, 1966), coating of tablets (Singiser, 1961) and granules (Wurster, 1959; Spitael and Kinget, 1977; Friedman and Donbrow, 1978), spray drying (Raff, Robinson and Svedres, 1961; Kornblum, 1969; Seager and Taskis, 1976) together with fluidised bed granulation (Wurster, 1960).

1.3.1 Fundamental Concepts of Fluidisation

When gas is blown through a layer of particles, a stage is reached where the upward gas flow is just sufficient to lift the powder particles. The bed expands and each particle is separated from its neighbours by a cushion of gas and all particles are in random, rapid motion (e.g. see Ridgway and Segovia, 1966). This state is termed fluidisation. During this state the powders behave in many respects like a liquid. The bed has a well defined surface which remains horizontal if tilted; dense objects sink and light ones float whilst a paddle can be rotated enabling a viscosity to be measured. It should however be noted that ordinary hydrostatic laws do not apply to the fluidised system.

The relationship between pressure difference across a powder bed with increased air velocity is illustrated using a generalised diagram in Fig 1.3. At low flow rates, air passes between the particles of powder without causing motion. As the velocity of air is increased the pressure drop (ΔP) rises (A-B). At B, the pressure drop multiplied by the cross-sectional area of the bed is equal to the force of gravity on the particles. In practice there is some degree of interparticulate arching and interlocking within the bed hence a slight amount of over pressure is necessary (C) before the bed breaks up and thus fluidises. Once this stage has been reached the gas velocity can be increased considerably with only a limited increase in pressure drop. As the velocity is further increased, the bed expands and bubbles form which rise through the bed and burst at the surface. Eventually as the velocity is increased the bed expands to the dimensions of the vessel and finally the particles are blown out of the system; a state termed pneumatic transport.

Fig. 1.3 Relationship between pressure drop across a bed of powder and increased gas velocity



(after Ridgway and Segovia, 1966)

1.3.2 States of Fluidisation

Various states of fluidisation can be identified depending upon the distribution of solid particles within the bed (Leva, 1959). The distribution is greatly affected by the choice of fluidising medium. "Particulate Fluidisation" is observed with water/solid systems and "Aggregative Fluidisation" with gaseous/solid systems.

Particulate Fluidisation has been characterised by the uniform, discrete, distribution of particles within the bed which is independent of time.

Aggregative Fluidisation exists when the particles in the bed are present not as individual discrete particles but aggregates. The gas rises through the bed primarily in the form of bubbles and within these bubbles there may be entrained solids. Hence the concentration of solids is not uniform throughout the bed. Several types of aggregative fluidisation are known (Leva, 1959) and these have recently been reviewed by Kulling and Simon (1980).

(i) Boiling Bed: this is a fluidised bed through which part of the fluidising medium passes in the form of bubbles approximately the same size as the solid particles but extremely small in relation to the dimensions of the vessel containing the medium.

(ii) Bubbling Bed: This occurs in a bed in which the bubbles are much larger than the suspended particles but are small in comparison to the dimensions of the vessel.

(iii) Slugging Bed: In narrow beds, bubbles may occupy the entire section of the vessel and divide the bed into several layers or slugs which are carried upward. During the upward motion, particles separate from the bottom of the slugs and fall back. Meanwhile new slugs are formed in the lower part of the fluidised bed.

(iv) Channelling Bed: this occurs when the fluidised medium forms vertical channels through which most of the fluid passes. During pharmaceutical fluid. bed drying this is a major problem since only localised overdrying occurs due to the partial fluidisation.

(v) Classifying Bed: is produced when particle mixtures of various densities or sizes are fluidised. Uniform concentration of particles is found only within horizontal planes.

(vi) Spouted Bed: is produced when the fluidising medium enters the bed through a single opening or a cross section much smaller than that of the bed. The fluid carries particles only in its central core with particles near the walls moving downwards. This type of bed is generally used for tablet coating.

1.4 FLUIDISED BED GRANULATION

Fluidised bed granulation describes the method of preparing tablet granules by spraying a solution (usually containing a binder) into a fluidised bed of powders. The technique was first described for pharmaceutical application by Wurster(1960) based on his earlier work of air-suspension coating (1959). Introduction of the method heralded a significant breakthrough in process technology since it eliminated many of the disadvantages associated with the multistage process of conventional wet granulation. The various stages of conventional wet granulation necessitate the use of numerous pieces of equipment to obtain the required mixing, agglomerating and drying (Table 1.2). This results in a very labour intensive process in comparison to the single stage operation in the fluidised bed granulator. While reviewing the process of fluidised bed granulation it is believed that an appreciation of the theoretical concept of fluidisation is necessary since this is the basic state in which

the three unit operations occur. This can be found in section 1.3. The advantages of such a system are indicated in Table 1.3 with the disadvantages shown in Table 1.4.

Since the first description of the apparatus and process by Wurster there has been a limited quantity of work published on this topic. However this has been performed on several different types and sizes of apparatus resulting in a number of inconsistencies in the literature.

1.4.1 Fluidised Bed Granulator Design

The fluid. bed granulator unit is primarily a design/development hybrid of the fluidised bed drier. A diagrammatic representation of a typical production unit is illustrated in Fig. 1.4. The granulator has an additional expansion chamber mounted above the product container to allow for bed expansion and also house the spray nozzle. The nozzle is supplied with compressed air for atomisation and binder solution under pressure to allow a range of addition rates.

The powders for processing are placed in the tapered product container. This container has an interchangeable screen together with a distribution grid to support the powders prior to fluidisation. During fluidisation the grid ensures correctly directed, equidistributed air immediately on entry to the bed. The use of various screens enables the pressure drop in front of the material to be optimised.

Air is either blown or sucked through the apparatus to attain fluidisation. The use of suction has advantages (Wolf, 1968) since:

(a) leaks are inwards thereby minimising hazards to personnel during processing of potent/toxic materials.

(b) inspection windows can be opened during the process thus allowing sample removal or material additions to be made.

(c) safety explosion flaps are self sealing therefore eliminating the need for a complicated locking procedure.

(d) aligning and equidistributing the air current can be effected along a short path.

(e) the unit can be compactly constructed thereby utilising a smaller floor space.

Table 1.2. Various stages of granule manufacture indicating apparatus necessary for traditional wet granulation and fluidised bed granulation.

STAGE	APPARATUS REQUIRED	
	TRADITIONAL WET GRANULATION	FLUIDISED BED GRANULATION
WEIGHING	BALANCE	BALANCE
DRY MIXING	MIXER	
WETTING/ KNEADING	MIXER/ KNEADER	
WET SCREENING	GRANULATOR	
DRYING	OVEN OR FLUID BED DRIER	FLUIDISED BED GRANULATOR
DRY SCREENING	MILL/ OSCILLATOR	
SCREENING		MILL/OSCILLATOR
LUBRICATING	MIXER	MIXER

Table 1.3 Advantages of fluidised bed granulation over traditional wet granulation.

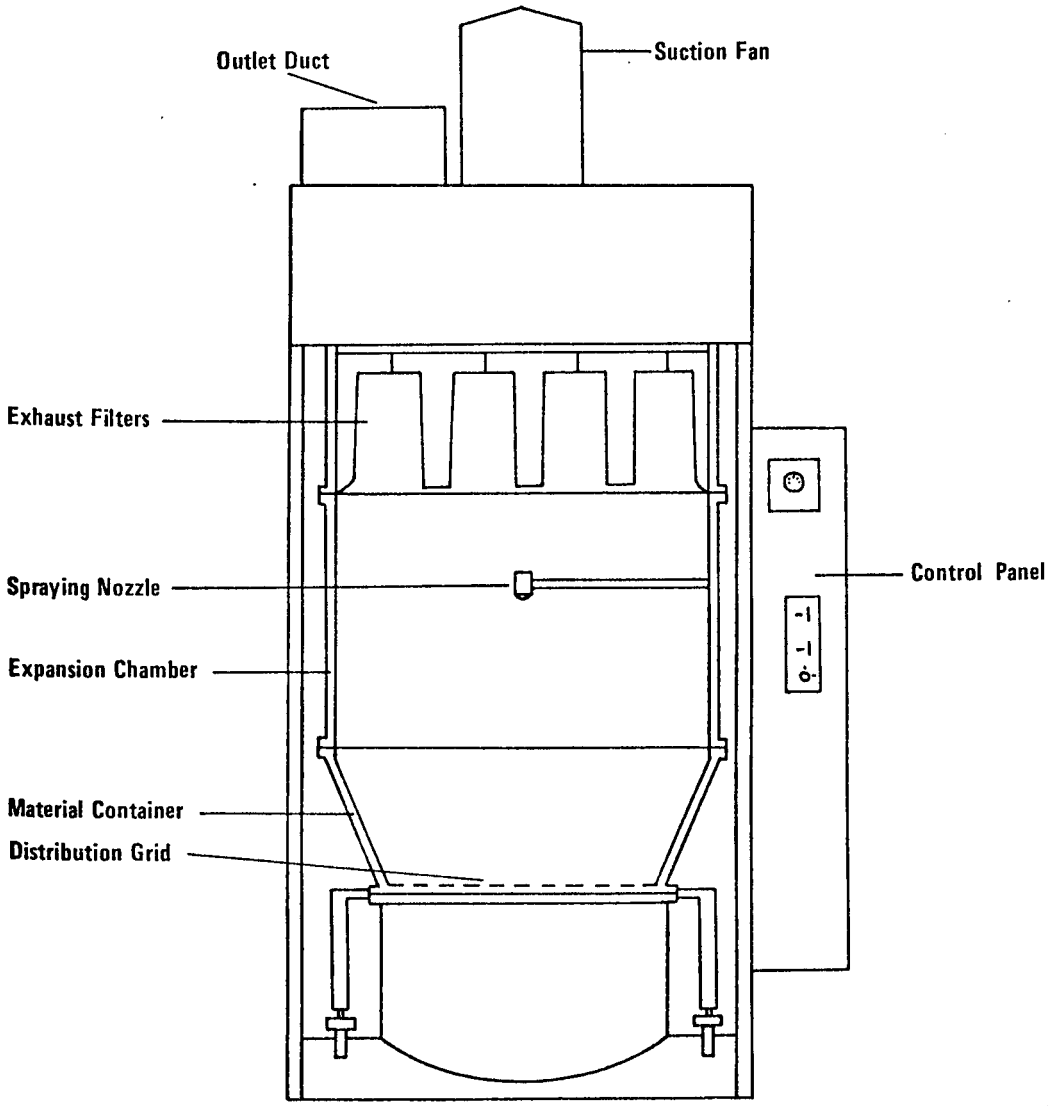
	WET GRANULATION	FLUIDISED BED GRANULATION
1.	Multistage operation requiring several pieces of equipment.	One piece of apparatus.
2.	Possible contamination from and to the operators.	All stages performed in an enclosed environment.
3.	Labour intensive, requiring at least 2 process operators.	Single operator.
4.	Relatively high process losses due to spillage. (Several transfer operations between various pieces of equipment.)	No transfer spillages.
5.	Several pieces of equipment utilising a large manufacturing area.	Single apparatus.
6.	Slow process due to number of manual steps.	Rapid Process.

Table 1.4 Disadvantages of fluidised bed granulation over traditional wet granulation.

	FLUIDISED BED GRANULATION	WET GRANULATION
1.	Process susceptible to slight variations in raw materials.	Fewer problems associated with raw material variations.
2.	Many formulations require extensive development time.	Relatively short development time.
3.	Extensive fine-tuning required during scale-up.	Minimal problems associated with scale-up.

Air is heated over large steam or electrical heat exchangers; air velocity is controlled by various flaps. Exhaust filters, to eliminate fine powder entrainment, are located axially, immediately above the expansion chamber. Filters are made of polyamide, polyethylene or cotton with woven-in carbon-pigmented yarn to dissipate any electrostatic charges. The filter hoses are mechanically jolted during processing to remove fines. This occurs intermittently and in conjuction with closure of the air flaps to interrupt the fluidising air supply and thus facilitate filter cleaning. The main chambers are manufactured from stainless steel and are thus robust and easy to clean.

Fig. 1.4. Basic Production Fluidised Bed Granulator Unit.



1.4.2 Fluidised Bed Granulation: A Chronology

In 1964 Scott and his fellow workers published the first article on Fluid Bed Granulation since Wurster's original paper in 1960. The theory and design considerations of the process were reviewed by using a fundamental engineering approach and employing mass and thermal energy balances. The basic design criteria were thus developed by analysing these balances and considering the rates of heat and mass transfer. Equations were developed from this approach and used

to predict relationships among a number of the process variables. A continuous production fluidised bed granulator was also described for the first time. Their second report published at the same time (Rankell et al, 1964) extended the theoretical basis to an evaluation of the operation and performance of a 30 kg capacity pilot model designed for both continuous and batch operation. A study of the process variables of air flow rate, air temperature, liquid flow rate, residence time and composition of granulating fluid was conducted. The influence of powder feed rate, nozzle location and the ability to produce a closely controlled granule size from the continuous mode of operation were also discussed. Granule samples produced from both modes of operation were compressed and the tablets evaluated.

Later, Contini and Atasoy (1966) published a short review of the advantages of the fluidised bed granulation process from a manufacturing and economic view point. The use of a 150 kg capacity model was also reported. A similar paper with limited technical content was published by Wolf (1968) which included a general overview of the mixing, wetting, drying, spray drying and agglomerating operations taking place within the FBG. The essential constructional features of the granulator, including product bowl design, fluidising air plate and distribution screen features were also discussed. During this period Liske and Mobüs (1968) compared the fluid. bed and wet granulation process. This was achieved by selecting various starch/lactose based formulations so that various binders and additional materials of widely differing density could be assessed. The processing of an un-named active ingredient in high and low concentration was also studied. The overall results indicated that materials processed by FBG produced finer, more free flowing and homogeneous granules which after compression produced harder and faster disintegrating tablets than materials processed by conventional wet granulation. A complete financial analysis of the cost saving over conventional wet massing was reported by Feigenbaum (1969). The analysis was based upon various capacity units (15, 30, 60, 120 kg) together with yearly material through-puts in a typical manufacturing environment with all costs calculated accordingly. The author reconfirmed the great cost saving potential of the process.

Published research on the process changed to a more technical approach in the last decade with more attention being paid to the influence of the various process variables upon the quality of final granule produced.

This more systematic approach began with a thesis by Thurn (1970) investigating in closer detail the mixing, agglomerating and drying operations which take place in the FBG process. Results indicated that the mixing stage was particularly influenced by air flow rate and air flow volume; the distribution of a small quantity of active substance in an inert base was used as a model. Statistical analysis of the results showed the random distribution nearing theoretical homogeneity. It was also indicated that the physical properties of the raw materials such as hydrophobicity may exert a strong influence upon the mixing stage. At the granulating stage particular attention was paid to the nozzle and it was concluded that a binary design gave a wide droplet distribution yielding a homogeneous granule. The need for powerful binders was recommended to aid granule formation and it was suggested that the wettability of the raw materials needed particular attention. It was concluded finally that granules displaying good flow and compression properties could be readily reproduced from this method. The drying stage was also investigated in some detail.

This thesis was perhaps the stimulus for a number of more detailed research articles investigating in greater depth the individual influence of process variables upon the quality and characteristics of the final product. Several series of papers on this topic have since been published and these will be reviewed in chronological order followed by an overall discussion.

In 1971, Bank, Bezzegh and Fekete reported experiments on a 300g laboratory and a 15 kg pilot scale model. The results from these experiments were used to establish the basic parameters for a more detailed study of selected parameters in a 120 kg capacity Aeromatic model. The parameters selected were quantity of binder, fluidising air flow rate and binder flow rate. The conditions for processing good quality granules were thus optimised and the granulator adapted for automatic control by using a punch card programme system. Finally it was shown that FBG granules produced tablets with more uniform physical characteristics (i.e. weight variation,

disintegration time). Ritschel (1971) published a short general review on the theory and equipment design of the technique, while Kala et al (1971) discussed the construction and mode of operation of a laboratory scale unit and compared FBG granulation with conventional methods.

During the same period Davies and Gloor (1971) published a paper describing the effects of process variables on the physical properties of the final granules. The variables investigated included binder solution addition rate, air pressure to the binary nozzle, inlet air temperature during the granulation cycle and nozzle position in relation to the air distribution grid. All the granules produced were subjected to standard tests including sieve size analysis, density and porosity determinations. This paper was followed by a further two articles in 1972 and 1973. Initially they reported the effects of various types of binders and binder concentrations upon granule and compressed tablet properties. In the final paper a detailed study into binder dilution effects on granule properties was presented.

Harada (1972), from material balances in a fluidised bed, derived a rate equation containing a coating rate growth coefficient and an agglomeration rate coefficient. The equation was used for calculating the particle diameter distribution and median diameters.

Gupte (1973) presented a model which was used to explain the effect of various factors that influence final size distribution. Factors discussed were initial weight of the powder charge, spray droplet size distribution in relation to atomising air pressure, binding agent and the drying time which was specifically related to temperature. Formulae enabling scale-up to be achieved were also presented.

A series of six articles were published next by a group of Hungarian researchers. The first paper by Ormós (1973) reviewed the methods and techniques intended for use in quantifying granule characteristics necessary to assess granulations produced by the FBG process. The remaining five papers in this series were published with fellow workers Pataki and Csukás. Initially the effect of quantity and addition rate of granulating solution were investigated together with concentration and amount of binding solution. The results

were evaluated and an equation derived to calculate the average particle size of the final granules (1973 a). The conclusions from this led to a further study into optimising the feed rate necessary to produce a quality granulation. A correlation was given for the maximum and equilibrium liquid feed rate on the basis of the heat and liquid balances of the process (1973 b). The effect of several operating parameters were assessed (1973 c): i.e. ratio of minimum bed height to diameter of bed, degree of expansion of the fluidised bed, degree of dispersion of the granulating liquid, distance of the atomising nozzle from the air distribution plate and the type of distributor upon the physical properties of the granulates produced. In their penultimate paper Ormós, Pataki and Csukás (1975 a) endeavoured to provide a theoretical description of the production of granulates together with a detailed account of the log normal distribution function and its application in classification of granule particle-size distributions. Correlations between the effect of changing process parameters on the particle size distribution parameters used to describe the resulting granulates were investigated. By the application of the log normal distribution function a calculation method was developed enabling the amount of granulating liquid and the granulation time to be optimised to produce a granule batch with good flow properties. Finally (1975 b) they assessed the effects of mechanical stirring of the fluidised bed during granulation. Several designs of stirrer were evaluated and it was concluded that the increased agitation eliminated channelling problems, ensured that the larger particles were in a partially fluidised state which allowed more granulating fluid to be added and decreased the porosity of the granules forming a stronger granule. A further report was published by Csukás and Ormós (1975) discussing the effect of the major process parameters upon the quality of granules from a continuous fluidised bed granulator. The experimental results were subjected to mathematical interpretation enabling the limits of application of the single bed continuous operation to be outlined.

Campy et al (1974) considered that no reliable scale up procedure had up until then been completely elucidated and proceeded to compare the air flow rates and air pressure distribution between a 5 kg and 30 kg capacity Glatt FBG. Static pressure measurements were made at

three points in the 5 kg and 30 kg models - beneath the distribution chamber, in the expansion chamber and above the exhaust filter. For both models the outlet valve had a greater effect on the air pressure than the inlet valve, and the pressure change across the distribution plate exceeded that across the exhaust filter. The maximum reduction in pressure achieved in the expansion chamber was greater for the 30 kg model than for the 5 kg model. This was considered a factor which could result in different drying rates on scale up.

Rouiller, Gurny and Doelker (1975) assessed a 1 kg Aeromatic FBG with regard to its suitability for producing granules of acceptable and reproducible size for tableting. Starch/lactose placebo mixes were granulated with aqueous or alcoholic binder solutions. Prioux et al (1975) studied the effect of fluidising air temperature, granulating solution addition rate and atomising air pressure using a 5 kg Glatt apparatus. Continuing the work on small scale fluidised bed granulation, Johnson, Rees and Sendall (1975) evaluated a 1 kg Aeromatic unit. They adopted a more mathematical approach studying the effects of fluidising air temperature, granulating solution concentration, addition rate and spray nozzle position upon final granule characteristics by means of an experiment of factorial design.

Growth of particles within the bed was examined by Shinoda et al (1976). A correlation was observed between the amount of binder solution adhering to the powder and the logarithm of the average particle size of the resultant granules. Particle growth of water soluble powders (lactose and mannitol) were observed to be faster than water insoluble powders (corn starch, crystalline cellulose). Thus indicating the importance of excipient hydrophobicity.

Mehta et al (1977) studied the influence of binder solution spray rate on granule size distribution in greater depth than had previously been reported. An explanation of the phenomena leading to experimental particle size distributions in a batch FBG was presented. Granulations made at various air speeds and granulating solution addition rates showed log normal distribution of particle size. The mean diameter was proportional to the square of the liquid flow rate but was independent of air flow rate. The standard deviation of particle size was, however, independent of both these parameters.

The bioavailability in rabbits of tablets prepared by FBG and direct compression were compared with a commercially available product by Ritschel and Erni (1977). Results showed that the experimental tablets made by FBG and direct compression gave slightly higher levels than the commercial tablet.

Motto (1977) reported that the FBG could be used to manufacture granules containing small quantities of active ingredients (e.g. hormones). This was confirmed by experimental assay showing that the final compressed product met Pharmacopoeial specification. A comparable, yet more detailed study into the fluid. bed granulation of a microdose pharmaceutical powder was published by Crooks and Schade (1978). The effects of solvent, binder addition rate and fluidising air temperature upon the granule size and drug distribution of 5% w/w phenylbutazone in a lactose powder mix was studied. Results indicated that as granule size increased so did the homogeneity of the phenylbutazone distribution. This was explained by the increased wetting of the larger granules which could then pick up the finer drug particles. This was aided by the phenylbutazone agglomerates being broken up by the ball milling action of the large granules.

An extremely important series of papers assessing specific areas of the technique in more detail has been published recently by Schaefer and Wørts (1977a,b; 1978a,b,c). Earlier Wørts (1972) had discussed the theories of wet and dry granulation, reviewed the various types of granulation equipment available and indicated the great potential of FBG. Initially Schaefer and Wørts (1977a) studied the effects of spray angle, nozzle height and starting materials on mean granule size and size distribution. The influence of the water absorption properties of the starting materials were shown to be an important factor; the need for a complete investigation using hydrophobic material was indicated as being necessary. An estimation of droplet size of atomised binder solution was reported next (1977b). This was achieved by using a droplet capture technique on a microscope slide covered with oil. Photography was used to reduce evaporation errors. The method suffers several disadvantages: it can only be applied to liquid flow rates below a certain value, reproducible sample collection is difficult and errors due to droplet flattening and spreading can occur. However the influence of binder and binder

viscosity, spray angle, mass ratio (ratio at the spray nozzle of the air-to-liquid mass) and liquid flow rate together with liquid nozzle orifice size upon spray droplet size and size distribution were measured using this technique. An empirical droplet size equation was derived which permitted an approximate prediction of the mass median diameter for the nozzle used in their experiments. This droplet size data was used later to evaluate the effects of binder solution and atomisation upon granule size and size distribution (1978b). Aqueous solutions of gelatin, polyvinylpyrrolidone, sodium carboxymethylcellulose and methylcellulose were used to prepare granules. Granule size was found to be directly proportional to binder concentration and a wide distribution was observed with increased droplet size. The type of binder was shown to affect granule size and this was attributed to the influence on droplet size and granule growth.

The effects of inlet air temperature and liquid flow rate on granule size and size distribution were investigated next by Schaefer and Wørts (1978a) together with the control of the moisture content of the granules in the drying phase. Granule size was found to be inversely proportional to the difference between inlet air temperature and wet bulb temperature in the granulation phase and directly proportional to the liquid flow rate. An increase in the amount of attrition during the drying phase was observed at increased air flow rates. At a range of experimental conditions a reproducible correlation was found between the moisture content of the granule and the difference between the product and wet bulb temperature. The theoretical aspects of this technique have been reported by Harbert (1974) whilst the correlation is well documented by the combined SIRA/ Industrial Pharmacy project group on Fluid. Bed Drying control of pharmaceuticals. The correlation has been shown to hold only for aqueous granulations (Banks, 1974).

The final paper by Schaefer and Wørts (1978c) examined the relationship under varying experimental conditions between quantity of binder solution and granule size and size distribution. Highest growth rates were obtained with the largest spray droplet size, fastest liquid flow rate, highest lactose content of the formulation and lowest inlet air temperature. These results were discussed and related to suggested growth mechanisms.

A further somewhat cursory study into granule growth was performed by Andreev et al (1980) using aminopyrine powder granulated with a methylcellulose solution. It was concluded that kinetic studies should allow the size enlargement and granule growth mechanisms to be explored.

1.4.3 Discussion of Fluidised Bed Granulation

The following discussion is arranged under various headings according to the classification of Ormós et al (1973a) and Schaefer et al (1977a) in Table 1.5.

Table 1.5. Classification of Fluid Bed Granulation Parameters

Product Parameters	Process Parameters	Apparatus Parameters
Starting Materials	Atomisation of Binder solution	Nozzle Height
Type of Binder	Bed Load	Air Distribution Plate
Binder Concentration	Spray Angle	Shape of granulator body
Quantity of Binder	Liquid Flow Rate	
Binder Solution Temperature	Fluidising Air Flow Rate	
	Fluidising Air Temperature	

1.4.3.a Product Parameters

A wide range of formulations have been processed during studies on the fluidised bed granulator, but only limited attention has been directed towards a study of the fundamental physico-chemical properties of the starting materials. There has been no published attempt to quantifying these properties, such as size, shape and density, although the influence of raw material hydrophobicity has received some cursory attention (Thurn, 1970; Shinoda et al, 1976). Several authors have expressed the need for a more detailed study into this area (Davies and Gloor, 1971; Schaefer and Wørts, 1977a).

The effect of the type and quantity of the binder has however received a great deal of attention. A wide range of binders have been used. Davies and Gloor (1972) have published a study directly comparing gelatin, acácia, PVP* and hydroxypropyl cellulose as binders. Various other binders including starch mucilage, methylcellulose and sucrose have also been reported (Rankell et al, 1964; Thurn, 1970;

*polyvinylpyrrolidone

and Mobüs
Johnson et al, 1975). Liske (1968), Thurn (1970) and Mehta et al (1977) have granulated with water after distributing dry binder into the starting materials; this resulted in a smaller sized granule. Generally all results concur that the physical properties of the fluidised bed granulation are strongly influenced by the type of binder. An increase in the binder concentration in the formulation increases binder adhesiveness yielding less friable granules of a larger average size. Aqueous granulating solutions were used in the above papers but Thurn (1970) and Rouiller (1975) have shown that a reduced granule size is produced when the binder is dissolved in an alcoholic solution.

The effect of binder dilution has been investigated since the quantity of solvent used in preparing a binder solution depends upon solution viscosity, solubility and desired granulating cycle time. The influence of the solvent quantity on the physical properties of the final granulation has been assessed by Davies and Gloor (1973) and Ormós et al (1973a). The former authors diluted three formulae concentrations of binder dissolved in two quantities of water. Results indicated that with an increase in dilution (quantity of solvent) there was a slight reduction in the final mean granule size. This was attributed to a decrease in the binder solution's tackiness or adhesiveness. Additionally they also found that binder dilution produced a less friable granule with a larger bulk density and improved flow properties. This was attributed to increased penetration and wetting of the fluidised solids by the binder solution.

The influence of granulating solution temperature has received limited attention. Thurn (1970) indicated that a high temperature should be used in order to avoid obtaining a coarse granulation. Schaefer and Wørts (1978b) have also suggested that binder solution temperature is a possible method of controlling spray droplet size and thus the final granulation characteristics.

On examination of the previous publications it is clear that the generalised conclusions relating to product parameters have been derived from a limited number of raw materials. Further work using a wider variety of material is considered necessary.

1.4.3b Process Parameters

Most of the published work on fluidised bed granulation has been carried out upon process parameters. Schaefer and Wørts (1977a) investigated the effect of spray angle and concluded that the diameter of the wetted surface area had no essential influence on granule size and size distribution. However at extremely small values of spray angle, a decrease in granule size was observed. Thurn (1970) also assessed spray angle although this was performed simultaneously with varying nozzle height thus a direct effect could not be determined.

Several authors (Bank et al, 1971; Davies and Gloor, 1971; Prioux et al, 1975; Johnson et al, 1975; Crooks and Schade, 1978) have found that adding a fixed volume of granulating solution at an increased liquid flow rate, results in a larger granule size. The latter authors also showed that the distribution of a microdose powder throughout the granules was improved. Rankell et al (1964) studied the effect of addition rate by increasing the feed rate whilst keeping the duration of the spraying constant. When these results are reprocessed to assess the effect of adding a predetermined volume of liquid comparable results are obtained. Schaefer and Wørts (1978a) suggested that since the experiments were carried out at unchanged values of nozzle air flow rate and air to liquid ratios then the effect of liquid flow rate might therefore be due to a change in droplet size. Two droplet sizes of gelatin solution were subsequently investigated and the effects of droplet size and liquid flow rate were found to have a significant effect on granule size. A linear correlation had previously been found (Rankell et al, 1964) between flow rate and granule size with the slope of the line dependent upon the type of binder. Thurn (1970) found no effect with increased fluid addition rate, while Ormós et al (1973a & b) reported a slight decrease in granule size.

The atomising air pressure governs the degree to which the granulating solution is broken up. Results from various investigations (Thurn, 1970; Davies and Gloor, 1971; Gupte, 1973; Prioux et al, 1975) have shown that an increase in the air pressure gives a corresponding fall in granule size. Ormós et al (1973c) however suggested that the mean particle size was not influenced to any appreciable degree by any large changes in the atomising air flow. An examination of the droplet sizes produced by changing atomising

air pressures was conducted by Thurn (1970), resulting in a simultaneous decrease in droplet size being found with increased pressure. A more detailed study into the effects of air pressure upon droplet size and thus granule size was subsequently carried out by Schaefer and Wørts (1977b, 1978b). The droplet sizes produced by atomising solutions of different binders were examined. It was concluded that varying droplet size was the simplest and most sensitive method of controlling final granule size since a linear correlation exists between droplet size and granule size.

The effect of varying fluidising air flow rate has received limited attention primarily due to the fact that variations cause excessive entrainment and exhaust air filter clogging. However Bank et al (1971) showed that an increase in air flow rate causes a decrease in average particle size. Various other authors (Scott et al, 1964 ; Liske and Mobüs, 1968; Ormós et al, 1973c) have also indicated the importance of the degree of bed expansion upon the final size distribution of the product. The decrease in granule size was attributed by Scott et al (1964) to the increased abrasion within the bed together with improved evaporation rates.

The inlet air temperature has been shown to exert a highly important influence upon granule quality (Rankellet al, 1964 ; Davies and Gloor, 1971; Johnson et al, 1975; Rouiller et al, 1975; Prioux et al, 1975; Crooks and Schade, 1978). An increase in temperature has been shown to produce a linear decrease in granule size (Schaefer and Wørts 1978a). Temperature changes also affect granule flow rate, friability and density. These have been attributed to an increased wetting of the fluidised powders by the binder solution as the temperature decreases.

1.4.3c Apparatus Parameters

The effect of changing the height of the spray nozzle above the air distribution grid has been investigated by several authors. Rankell et al (1964) showed that there was an increase in mean particle size as the nozzle height was decreased. Davies and Gloor (1971) while confirming this observation also concluded that there were no significant changes in the final granulation densities or flow properties. Later Ormós et al (1973c) found evidence that nozzle

location seemed only to influence granule size distribution and not granule size. This was later confirmed by Schaefer and Wørts (1977a). Several authors (Thurn, 1970; Johnson et al, 1975) have found however that nozzle location has no effect upon the final granulation.

The importance of the distribution plate was indicated by Wolf (1968) since it ensures efficient equidistribution of fluidising air thus avoiding areas of only localised fluidisation. The results of Ormós et al (1973c) revealed that the mean granule size, mean porosity and particle size distribution of the final granulation was practically independent of the design of the air distributor. Changes in the design of the shape of the granulator body itself have not been documented. The basic early design which includes an expansion chamber has remained unchanged.

Experience during scale up from laboratory to production equipment has received limited attention and this lack of information perhaps accounts for the somewhat anomalous results reported by various authors. Gupte (1973) however tentatively published formulae to enable scale up to be carried out for the fluidised bed granulation process whilst Campy et al (1974) presented the air flow rates and air pressure distribution data for 5 kg and 30 kg capacity units.

1.4.3d Safety

The potential safety and air pollution problems associated with fluidising techniques have been well documented (Kulling, 1976; Simon, 1978; Kulling and Simon, 1980) specifically by the commercial suppliers of such units in order to conform to local health and safety legislative standards.

1.5 SCOPE OF THE THESIS

The implementation by the pharmaceutical industry of the Fluidised Bed Granulation process has never reached the early expectations due to the problems of transferring apparently trouble free conventionally wet granulated formulations to the equipment. This variability is perhaps in some ways supported by the number of conflicting results in the published literature. Many workers have investigated the same parameters and found anomalous data.

The first part of this thesis was aimed at identifying and quantifying the influence of the major variables in a statisically designed series of experiments. This method of investigation also enabled the extent of variable interaction to be documented giving a clearer understanding of the variableinterrelationships thus forming a sound basis for a more fundamental study into the process.

Traditionally the measurement of granule properties has been employed to evaluate parameter changes by the use of standard well-documented techniques. The measurement of the torque generated during the stirring of granules in a mixer is considered to be a simple method of classifying granule quality. A novel test apparatus is presented to quantify this measurement and the data correlated with traditional methods.

Few workers have considered the interaction between the binder solution droplets and the powder particles. This has been due to the difficulties in easily and accurately measuring the droplet size distribution of the spray. A study into the influence of the droplet is considered essential since the droplet is one of the key components of the growth mechanism. Techniques for accurately measuring the droplet size have been reviewed with the use of a light scattering technique providing a platform for this study. Current literature presupposes that during droplet/particle collision the powder particles are completely wetted thereby successfully forming a strong combination reaching perhaps funicular or capillary states. However many drugs are hydrophobic thereby presenting a major problem during aggregate formation. An investigation quantifying this aspect is presented together with the use of surfactants to reduce this hydrophobicity. The method of surfactant addition is considered important since when dissolved in the binder solution it affects spray/droplet characteristics, and thus the droplet/particle combination.

The formation of the droplet/multiparticle combination has not received any detailed attention primarily due to the absence of methods of monitoring such a system. It is believed that a study of the binder distribution will aid an investigation into the fundamental mechanism. To achieve this aim a fluorescent labelling technique was pioneered to enable a quick visible method of monitoring distribution particularly in the near dried aggregate. Further more detailed

methods of assessing structure will be employed specifically based upon solvent extraction procedures combined with scanning electron microscopic analysis. These techniques together with sieve analysis data will be used to assess various model formulations during processing in the Fluid Bed Granulator.

The general aim of this thesis was to attempt to explain the basic mechanisms of the process of FBG thus providing a scientific platform for formulators to optimise future formulations.

CHAPTER 2

MATERIALS AND METHODS

2.1 MATERIALS
2.1.1 Lactose B.P.
2.1.2 Maize Starch B.P.
2.1.3 Polyvinylpyrrolidone (PVP)
2.1.4 Magnesium Stearate B.P.
2.1.5 Salicylic Acid Powder B.P.
2.1.6 Fluorescein Isothiocyanate (FITC)
2.1.7 Sodium Lauryl Sulphate (SLS)
2.1.8 Heavy Magnesium Carbonate B.P.

2.2 THE FLUIDISED BED GRANULATOR
2.2.1 The Aeromatic Fluidised Bed Dryer (FBD)
2.2.2 Conversion to a Fluidised Bed Granulator (FBG)
2.2.3 General Operating Procedure for the FBG

2.3 STANDARD TEST METHODS FOR SOLUTIONS
2.3.1 Du Nuoy Tensiometer
2.3.2 Weight per Millilitre (Density)

2.4 TEST METHODS FOR GRANULES
2.4.1 Size Distribution
2.4.2 Granule Bulk Density
2.4.2.a Method of determining Poured (Bulk) Density
2.4.2.b Method of determining Tap Density
2.4.2.c Hausner Ratio
2.4.3 Angle of Repose
2.4.4 Flow Rate
2.4.5 Torque Measurement

2.5 BINDER TRACING TECHNIQUES FOR GRANULES
2.5.1 Fluorescent Tracing
2.5.1.a Binder/Fluorochrome Conjugation
2.5.1.b Conjugation Process
2.5.1.c Conjugate Purification
2.5.1.d Determination of PVP concentration in samples collected
2.5.1.e Ultrafiltration as a method of conjugate purification
2.5.1.f Application
2.5.1.g Fluorescent Microscopy
2.5.2 Solvent Extraction
2.5.2.a Fluidised bed extraction
2.5.3 Examination by Scanning Electron Microscopy

2.6 GRANULE COMPRESSION

2.7 STANDARD TEST METHODS FOR TABLETS
2.7.1 Crushing Strength
2.7.2 Thickness
2.7.3 Weight Variation
2.7.4 Friability
2.7.5 Disintegration
2.7.6 Dissolution

CHAPTER 2

MATERIALS AND METHODS

2.1 MATERIALS

The following materials were used in this work.

2.1.1 Lactose B.P.

Lactose is the monohydrate of 4-O-β-galactopyranol-α-D-glucopyranose. It is a white, crystalline powder, odourless, with a faintly sweet taste, freely soluble in water but practically insoluble in alcohol. In tablets it is the principal substance employed as a bulking agent. It is relatively inexpensive and is available commercially as coarse granular (180 - 250 μm) and regular grade (150 - 180 μm). It is stable and does not react with most medicinal substances. Its rapid solubility means quick release of the drug substance that it carries.

Lactose crystals easily compact into tablets. It is not hygroscopic and readily dries after wet granulation. It has a high melting point (202°C) so that the bulk material is not softened by the frictional forces of compression.

Spray dried lactose is also used as a directly compressible substance (Gunsel and Lachman, 1963). The particles are roughly spherical or may consist of spherical aggregates which flow well. When spray dried lactose is manufactured, a portion of it is produced in a microcrystalline form and some dries in an amorphous or glass state. This combination of microcrystals and amorphous solids produces a form that has good compressibility. Spray dried lactose has the disadvantage that it is more susceptible to browning upon storage, than powdered lactose, due to the presence of free 5-(hydroxymethyl)-2-(furaldehyde) (Brownley and Lachman, 1964).

The lactose B.P. used in this work was supplied by Whey Products Ltd.

2.1.2 Maize Starch B.P.

Maize starch consists of amylose and amylopectin, both polysaccharides based on α-glucose. It is obtained from the grains of maize (Zea mays L.) as a fine white powder which creaks when pressed between the fingers and is odourless, tasteless and practically insoluble in cold water and alcohol. Starches play an important role in pharmaceutical tablets as bulking agents, binders and disintegrants. When included as part of the granule they aid disintegration of the granules into which a tablet breaks up. This action was thought to be due primarily to the swelling of the starch on contact with water, although it has been shown that it only swells 5 -10% in mean diameter on contact with water at 37°C (Ingram & Lowenthal, 1966). The disintegrating force can also be attributed to capillary action (Curlin, 1955) although specially modified starches (McKee & Herbst, 1962) are available commercially, such as sodium starch glycolate, which swell significantly and are thus more useful.

Although starches contain 12 - 14% moisture they tend to stabilise hygroscopic drugs and protect tablets of such materials from deterioration before use. Not only are starches useful diluents but, as pastes they make good binding agents particularly when drugs are insoluble and in high concentration. The supply of maize starch B.P. was obtained from Charnwood Pharmaceuticals.

2.1.3 Polyvinylpyrrolidone (PVP)

PVP consists of essentially linear polymers of 1-vinylpyrrolid-2-one. Variation in the degree of polymerisation results in the production of polymers with different chain lengths. Commercial grades usually bear a 'K' number which is derived from the viscosity and is related to molecular weight.

PVP is a white or creamy-white, odourless or almost odourless, hygroscopic, tasteless powder which is readily soluble in water and a wide range of organic solvents as well as in gastric and intestinal fluids. It is a well known material most commonly used pharmaceutically as a tablet binder and occasionally in film coating. A tablet binder is a substance which glues powders together and causes them to form granules. The quantity of binder is important since it must be carefully regulated because the tablet must hold together

until swallowed and must then disintegrate to release the medicament.

PVP has excellent adhesive qualities and is extremely tacky while drying. It is soluble in water and some organic solvents; it is therefore possible to bond particles of a water sensitive drug with organic solvent yet still obtain release of the medicaments in aqueous environments. In comparative studies with other common binding agents PVP was shown to be an effective, stable binding agent and was comparable to or better than other agents (Lehrman & Skauen, 1958).

The PVP used in this work was PVP K29/32 with a molecular weight of 37,500 (Collett & Kesteven, 1978) supplied by Gaf (GB) Ltd.

2.1.4 Magnesium Stearate B.P.

Magnesium stearate is the magnesium salt of a commercial stearic acid which consists chiefly of a mixture of stearic and palmitic acids. It contains the equivalent of not less than 6.5% and not more than 8.5% MgO calculated with reference to the dried weight.

It is a fine white bulky powder having a faint characteristic odour. It is unctuous, adhering readily to the skin and free from grittiness; it is insoluble in water, alcohol and ether.

Magnesium stearate is often added in the last mixing stage before compression, as a lubricant. True lubrication is particularly required immediately after compression of the tablet within the die to reduce the friction between the inner die wall and the tablet edge during the ejection cycle. Lubricants help the granules to slip and slide during the formation of the compact as well as to facilitate the ejection of the tablet.

In concentrations of less than 1%, magnesium stearate is an excellent lubricant, has good antiadherent properties but is a poor glidant. It is used most effectively in a fine degree of subdivision (i.e. 50 μm or less) since it can cover a greater area of the surface of the granulation.

The super fine grade of magnesium stearate used in this work was supplied by Witco Chemicals Company.

2.1.5 Salicylic Acid Powder B.P.

Salicylic acid powder B.P. is a white powder with a sweetish

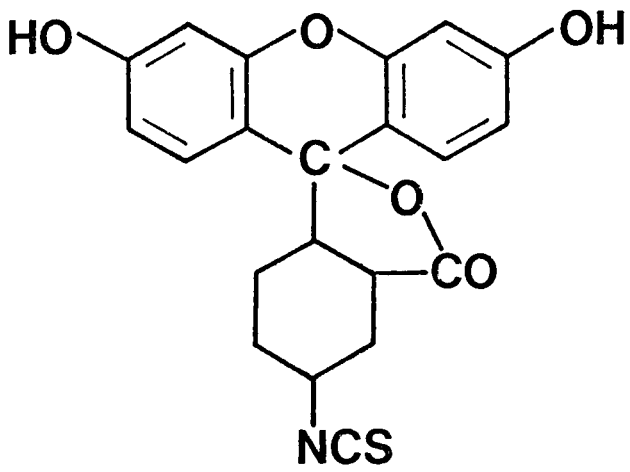
acrid taste. It is almost odourless, but its dust irritates the nasal membrane. Although insoluble in water it is readily soluble in ether and chloroform.

Salicylic acid is used medically in concentrations of between one and forty percent as a keratolytic substance with bacteriostatic and fungicidal properties.

It was selected in these studies as being a model hydrophobic compound since it has a contact angle of 103° (Lerk et al, 1976). The supply of salicylic acid was obtained from Evans Medical.

2.1.6 Fluorescein Isothiocyanate (FITC)

Structure



It is a bright yellow, slightly hygroscopic powder and is available commercially as two isomers of which isomer I is the most fluorescent. FITC was first introduced by Riggs et al (1958) and has greatly simplified fluorescein conjugation. It is extensively used by immunologists for protein (including antibody) tracing since under irradiation with ultra-violet light it produces a brilliant green fluorescence.

Fluorescein isothiocyanate, isomer I, was used in this work and supplied by Sigma London Chemical Company Limited.

2.1.7 Sodium Lauryl Sulphate (SLS)

Sodium lauryl sulphate is a mixture of sodium alkyl sulphates consisting chiefly of sodium dodecyl sulphate, $C_{12}H_{25}O.SO_2.Na$. It is a white or pale yellow sternutatory powder or crystals with a slight characteristic odour. SLS is an anionic emulsifying agent and used in pharmacy not only for solubilisation but also for wetting and the interfacial stabilisation of emulsions and suspensions.

It was selected in this study as a model surfactant to reduce interfacial tension and thereby improve wetting. The supply of SLS was obtained from British Drug House Chemicals Ltd.

2.1.8 Heavy Magnesium Carbonate B.P.

Heavy magnesium carbonate is a hydrated magnesium carbonate of varying composition corresponding approximately to the formula $3MgCO_3$, $Mg(OH)_2$, $4H_2O$ and containing the equivalent of 40 to 45% MgO. It is a white odourless tasteless powder and is commonly used as a weak antacid or a mild laxative.

In this study it was used as a model tablet excipient as employed by Ridgway and Rubinstein (1971). The heavy magnesium carbonate B.P. was supplied by British Drug House Chemicals Ltd.

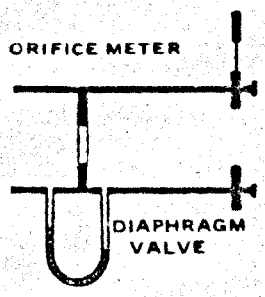
2.2. THE FLUIDISED BED GRANULATOR

2.2.1 The Aeromatic Fluidised Bed Dryer (FBD)

At the beginning of the project an Aeromatic FBD was available. For the plan of work proposed it was necessary to convert it into a fluidised bed granulator. The basic drier unit was the Aeromatic STP 2 fluidised bed drier of 1 kg capacity. This is shown in Fig. 2.1. Fluidisation is produced when an air stream induced by the fan in the upper part of the cabinet is drawn through an air heater and pre-filter. After heating has been completed the filtered hot air passes upwards through the distribution grid and a 250 μm stainless steel screen at the bottom of the product container, bringing the product into a fluidised state. Above the product container a nylon filter prevents fine particle entrainment losses as the air exits through the exhaust duct to a fume cupboard. Attached to the filter frame is a mechanically activated shaking device which removes fine particles adhering to the filter surface. In addition the equipment was fitted with a timer for setting the drying time, a potentiometer for setting the drying temperature, thermometer for recording inlet air temperature and a thermometer for recording the outlet air temperature.

2.2.2. Conversion to a Fluidised Bed Granulator (FBG)

The conversion of the Aeromatic FBD into an instrumented fluidised bed granulator necessitated the following changes.


ORIFICE METER
DIAPHRAGM VALVE

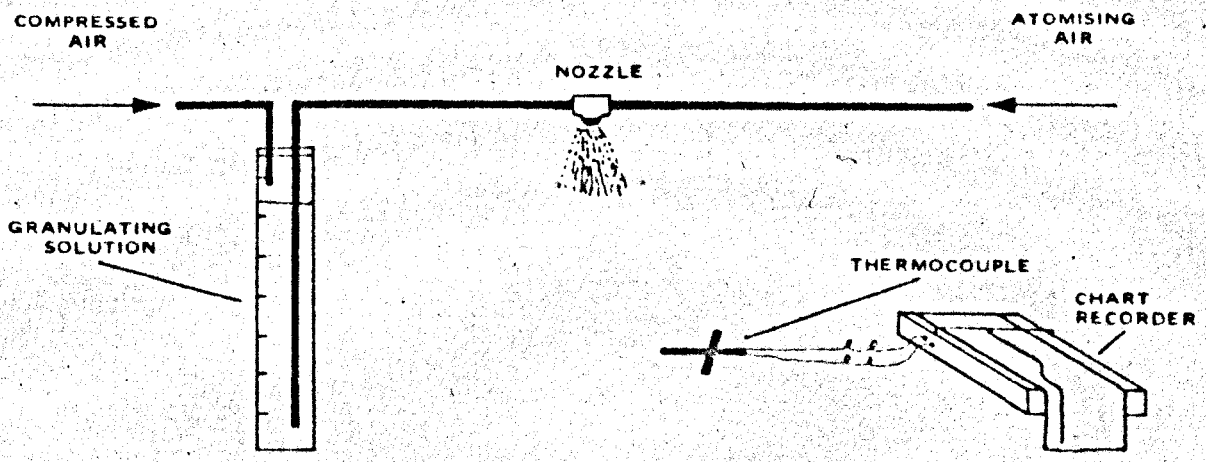

COMPRESSED AIR
ATOMISING AIR
NOZZLE
GRANULATING SOLUTION
THERMOCOUPLE
CHART RECORDER

Fig. 2.1 The Aeromatic Fluidised Bed Dryer (showing conversion to an instrumented fluidised bed granulator).

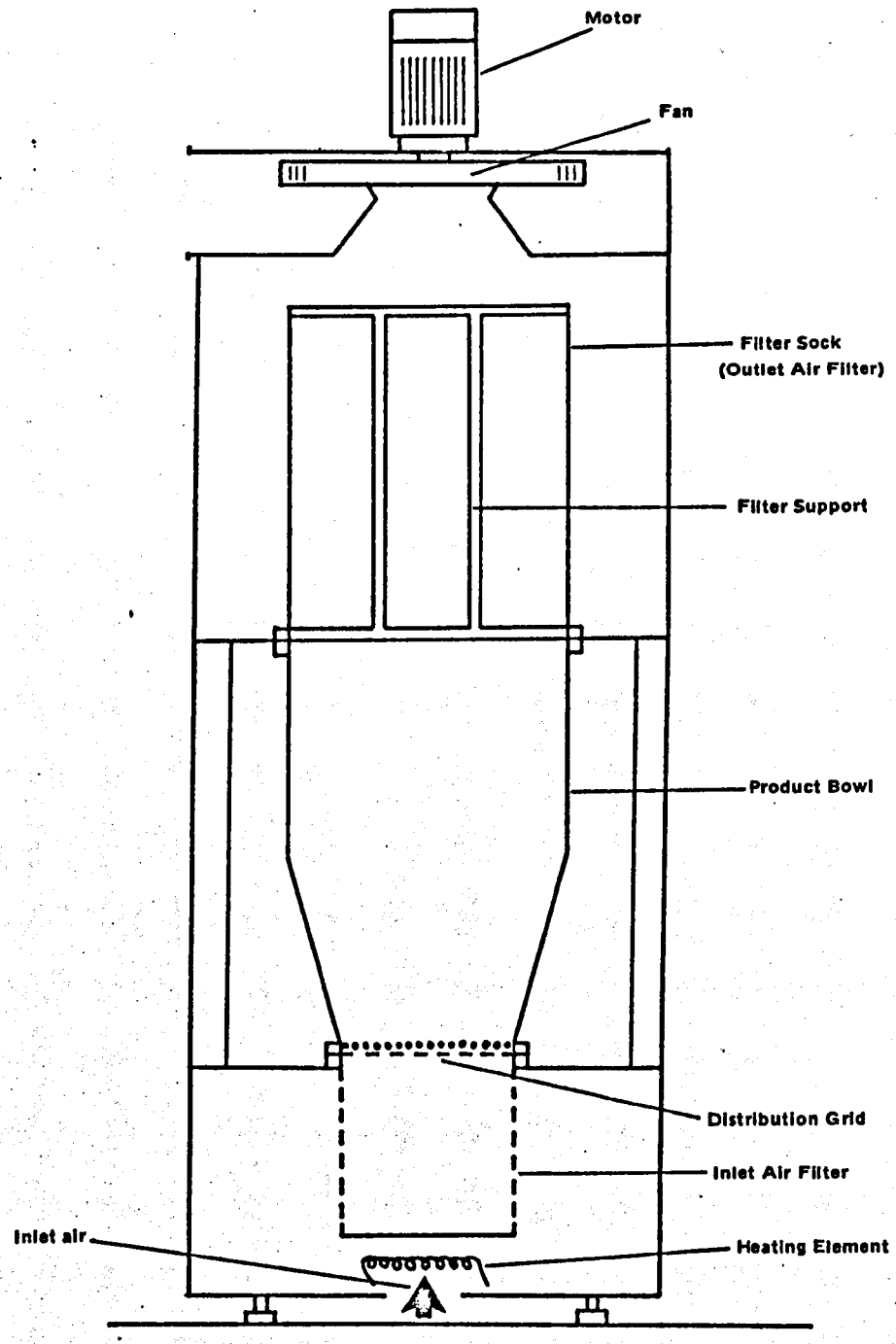
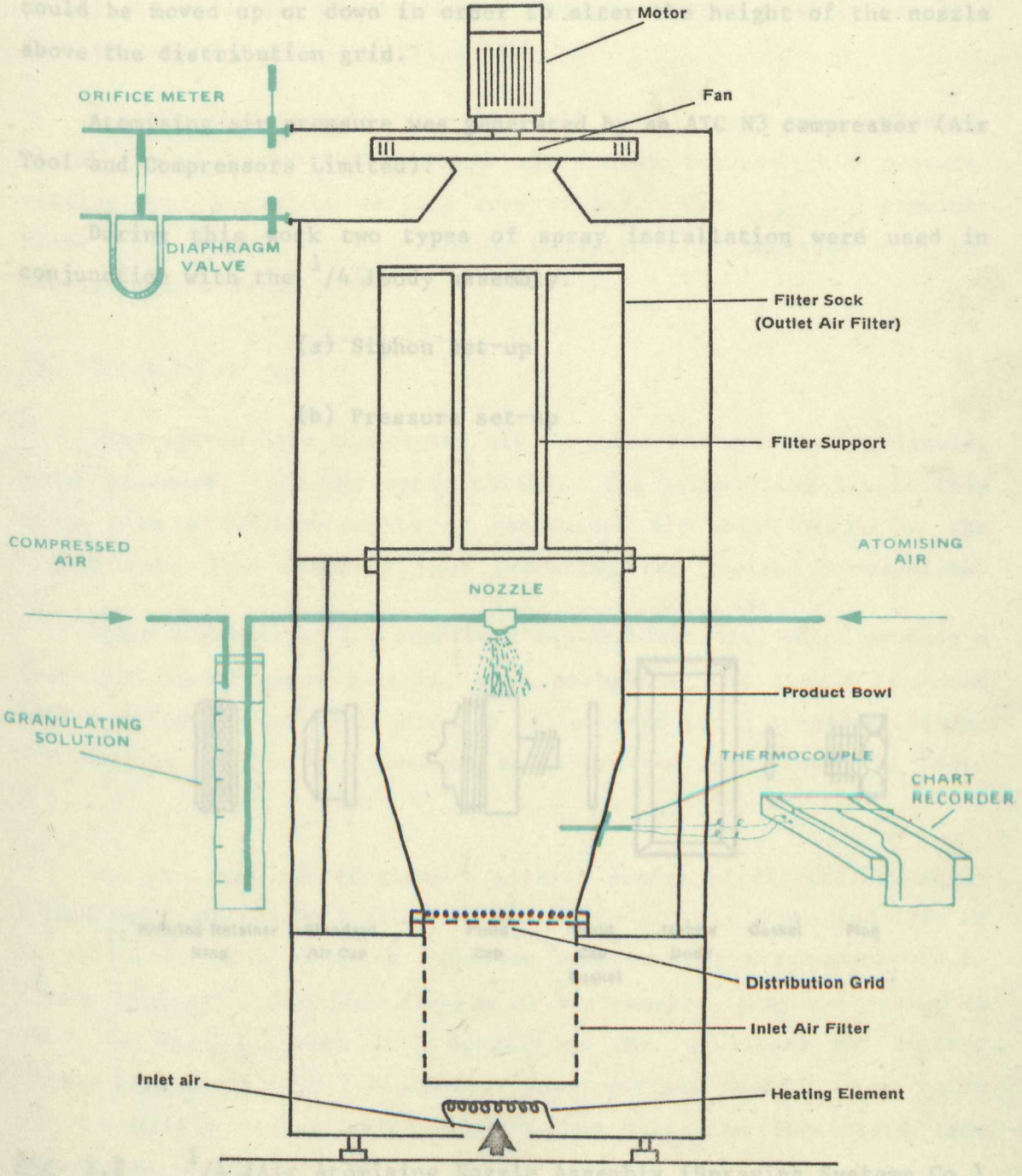


Fig. 2.1 The Aeromatic Fluidised Bed Dryer (showing conversion to an instrumented fluidised bed granulator).



(i) Addition of a spray nozzle

An air atomising nozzle body assembly was used; this mixes compressed air with a liquid to provide fine atomisation. The nozzle was composed of a $^{1}/_{4}$ Jseries body assembly (Spraying Systems Company) with interchangeable air and fluid caps. The complete unit is shown in Fig. 2.2.

The spray nozzle was mounted to spray downwards inside the product bowl; it was positioned centrally by a support bracket which could be moved up or down in order to alter the height of the nozzle above the distribution grid.

Atomising air pressure was generated by an ATC N3 compressor (Air Tool and Compressors Limited).

During this work two types of spray installation were used in conjunction with the $^{1}/_{4}$ Jbody assembly.

(a) Siphon set-up

(b) Pressure set-up

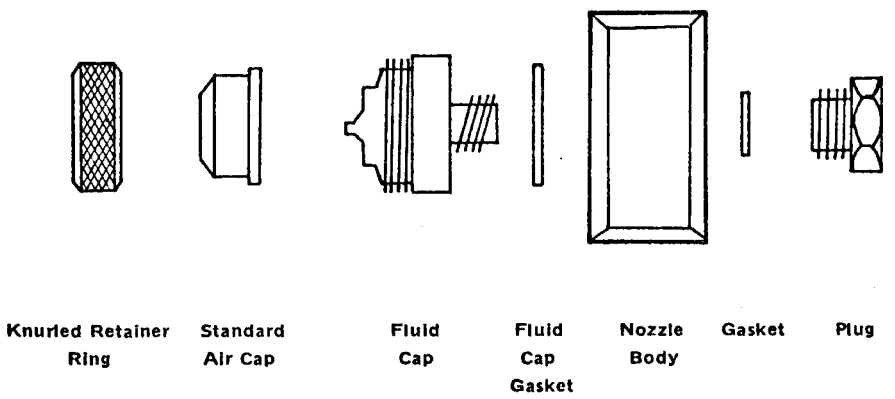


Fig. 2.2 $^{1}/_{4}$ JAir Atomising Nozzle Assembly (Spraying Systems Co.)

(a) Siphon set-up

Spraying was carried out using the siphon mode. Granulating solution was drawn into the spray nozzle by suction created by the flow of the atomising air through the nozzle body. Before entering the spray nozzle the atomising air is filtered and passed through a pressure regulator (Watts No. 549.2) fitted with a pressure gauge (Watts 1-8 bar). A constant siphon head of 100mm was maintained throughout the runs by continually monitoring the granulating solution height and adjusting as necessary. The granulating solution was held in a thermostatically controlled bath.

A range of different types of fluid and air caps were evaluated. A full round spray cone pattern was chosen because this produced wetting over a maximum surface area of bed. The combinations tested are listed in Table 2.1, together with the manufacturer's data.

(b) Pressure set-up

This system uses compressed air to force the granulating liquid, under pressure, into the spray nozzle. The granulating liquid then mixes with a further supply of compressed air which breaks up the liquid into fine droplets thus producing the desired atomisation.

Again a series of air cap/fluid cap combinations, which produce a full cone round spray pattern, were evaluated. It should be noted that a different design of air cap is required for a pressure system. The details of the combinations actually used are listed in Table 2.2.

The pressure system gives a greater degree of flexibility enabling a more controllable fluid addition rate and air atomising rate to be obtained. The addition rate was monitored by a rotameter (G.A. Platon Limited). The flow diagram of the complete pressure set-up is shown in Fig. 2.3 with full details of the regulators and filters (Watts Regulators (U.K.) Limited). One important feature to be noted is the safety valves which protect the precision regulators from excess pressure.

Table 2.1.

Fluid and Air Cap Combinations together with Manufacturer's Technical Data (Spraying Systems Company) for the SIPHON Set-up

Manufacturer's Spray Set-up Ref. No.	Air Cap Ref. No. A.N.	Fluid Cap Ref. No. F.N.	Spray Cone Angle	Data for 1.67 bar Atomising Air Pressure		Estimated Data for 2.67 bar Atomising Air Pressure	
				Distance over which cone angle is maintained (mm)	Flow Rate ml s^{-1}	Distance over which cone angle is maintained (mm)	Flow Rate ml s^{-1}
1A	64	1650	18°	279	0.20	286	0.31
1	64	2050	18°	305	0.35	343	0.51
2A	70	2050	18°	305	0.38	343	0.53
2	70	2850	21°	380	0.49	419	0.82
4	120	60100	17°	103*	7.2*	470	2.96

*Manufacturers estimated values

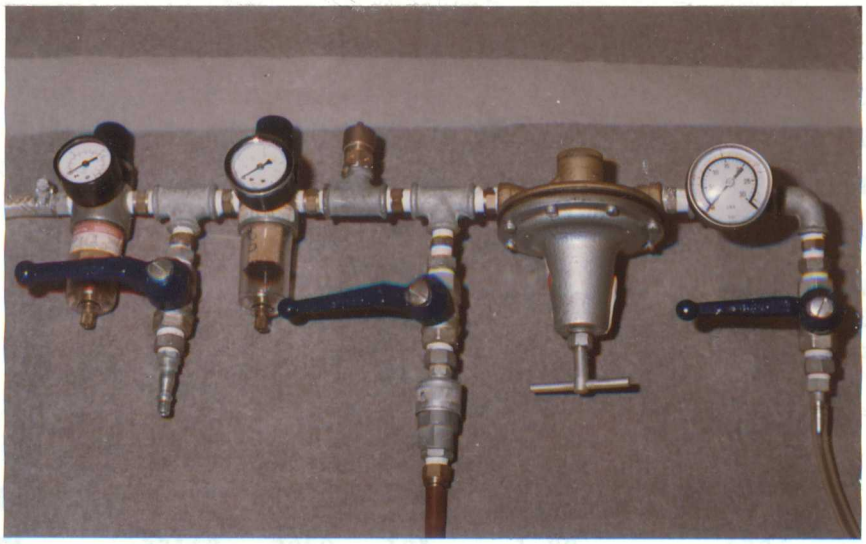
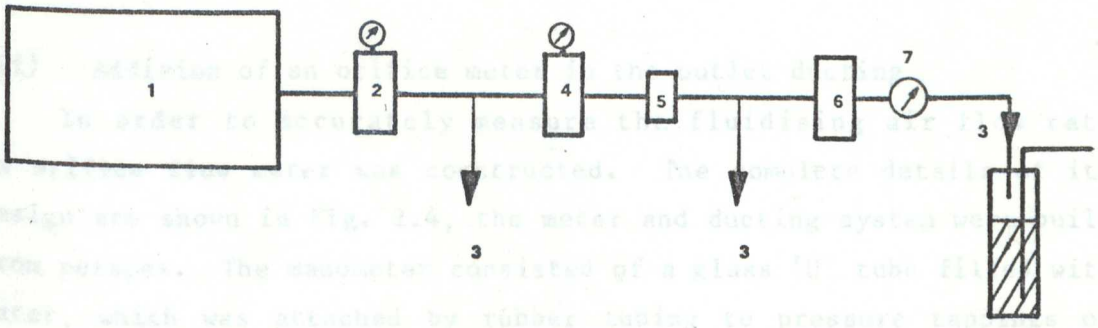


Fig. 2.3 Compressed Air Control System



1. Air compressor and receiver tank (Model: ATC-N3).

2. Watts miniature integral filter regulator with automatic drain No. 549.2, Serial No. 7608 with pressure gauge (1 - 11 bar).

3. Lever gate valve with PCL quick relief connections.

4. Watts miniature integral filter regulator with automatic drain No. 549.2, Serial No. 7605 with pressure gauge (1 - 5 bar).

5. Watts adjustable safety valve.

6 Watts precision regulator, No. 216.2, Serial No. 7610 (1 - 1.53 bar).

7. Watts pressure gauge (1 - 2.3 bar).

Table 2.2

Fluid and Air Cap Combinations, together with Manufacturer's Technical Data (Spraying Systems Company) for the PRESSURE Set-up

Manufacturers Spray Set-up Ref. No.	Air Cap Ref. No. A.N.	Fluid Cap Ref. No. F.N.	Spray Cone Angle	Atomising Air Pressure (bar)	Data for Liquid Pressure at 1.67 bar	
					Distance over which cone angle is maintained (mm)	Flow Rate $ml\ s^{-1}$
11	67147	2050	13°	1.80	305	0.58
12A	73160	2050	12°	1.80	432	0.58
12	73160	2850	12°	2.47	483*	1.35*

*Estimated values

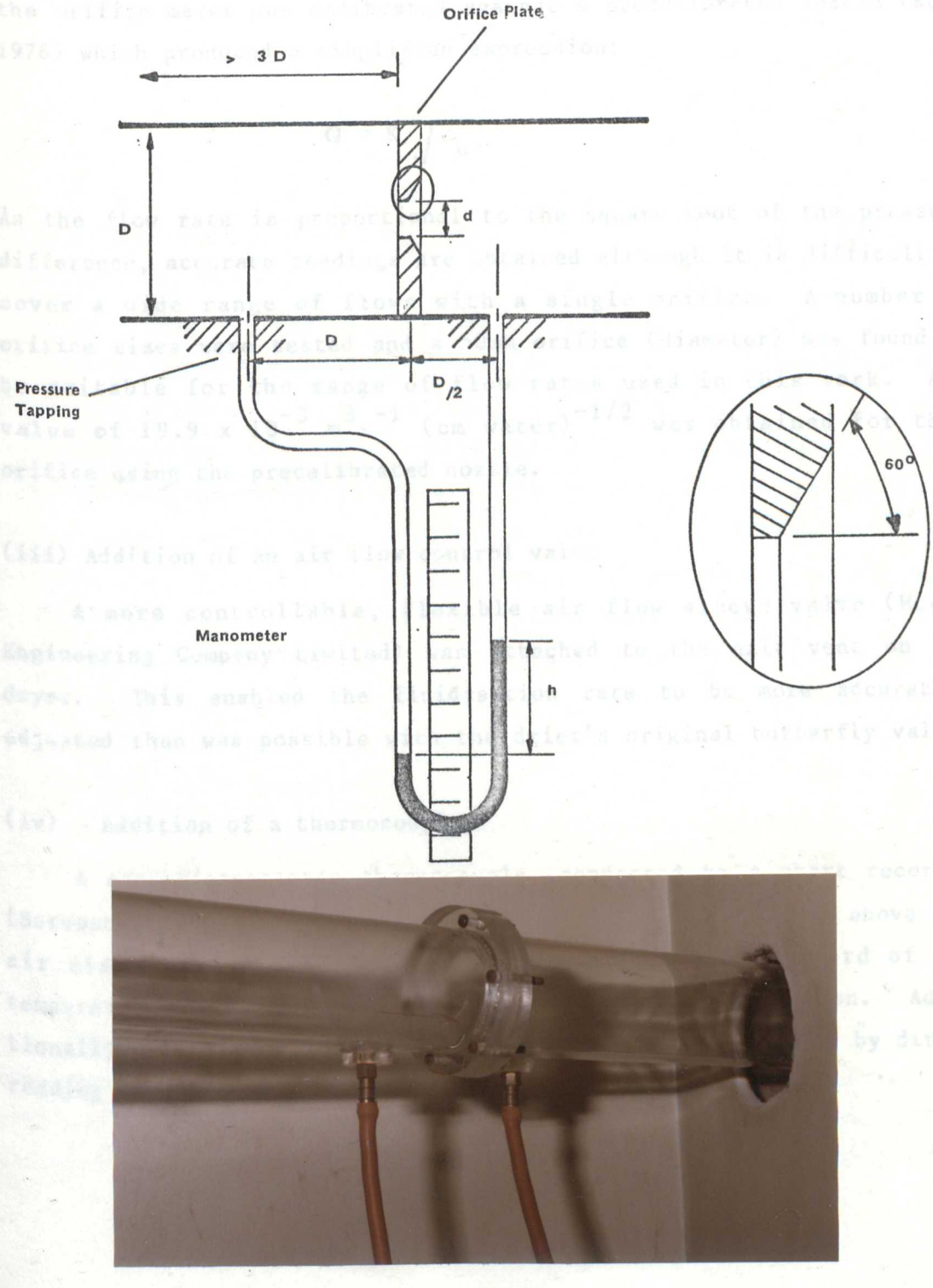
(ii) Addition of an orifice meter in the outlet ducting

In order to accurately measure the fluidising air flow rate an orifice flow meter was constructed. The complete details of its design are shown in Fig. 2.4, the meter and ducting system were built from perspex. The manometer consisted of a glass 'U' tube filled with water, which was attached by rubber tubing to pressure tappings on either side of the orifice plate. The upstream tapping was situated one pipe diameter, and the downstream tapping half a pipe diameter from the orifice. A control valve (section iii) was connected to the inlet ducting and the complete system attached to the exit vent of the drier.

The flow rate is obtained from the pressure difference at the manometer. By applying energy and balance equations an expression for flow rate can be derived (Coulson and Richardson, 1964). A simplified form for a horizontal orifice meter in which the orifice area is small compared with the area of the pipe is given as

$$Q = C_D A_o \rho\sqrt{2gh_o}$$

Fig. 2.4 Orifice Meter Design



where Q is volumetric flow rate, C_D is coefficient of discharge, A_o is area of flow at orifice, ρ is density of air, g is gravitational constant and h_o is fall in head over the manometer.

This equation contains an expression C_D which takes into account frictional losses dependent upon Reynolds Number, roughness of the pipe walls, shape of the orifice, thickness of the orifice plate and the meters proximity to bends and valves. Since C_D is not a simple expression it cannot be calculated. To overcome this difficulty, the orifice meter was calibrated against a precalibrated nozzle (Rue, 1976) which produced a simplified expression:

$$Q = K \sqrt{h_o}$$

As the flow rate is proportional to the square root of the pressure difference, accurate readings are obtained although it is difficult to cover a wide range of flows with a single orifice. A number of orifice sizes were tested and a 50mm orifice (diameter) was found to be suitable for the range of flow rates used in this work. A K value of 19.9×10^{-3} $m^3 s^{-1}$ $(cm\ water)^{-1/2}$ was obtained for this orifice using the precalibrated nozzle.

(iii) Addition of an air flow control valve

A more controllable, flexible air flow sleeve valve (Mucon Engineering Company Limited) was attached to the exit vent on the dryer. This enabled the fluidisation rate to be more accurately adjusted than was possible with the drier's original butterfly valve.

(iv) Addition of a thermocouple

A copper/constantan thermocouple, connected to a chart recorder (Servoscribe) was attached to the product container 150mm above the air distribution plate. This enabled a permanent record of the temperature within the bed to be made for each granulation. Additionally the outlet and inlet temperature could be monitored by direct reading of the dryer's thermometers.

2.2.3 General Operating Procedure for the FBG

The powder charge was presifted through a 1000 μm sieve (to remove any lumps), weighed and added to the product container after the inlet air temperature had stabilised at the run value. Prior to the addition of granulating solution the powders in the container were mixed by fluidisation for thirty seconds. The mechanical filter shaker was activated every two minutes during a run.

After this premixing the granulating solution was sprayed onto the fluidised bed at the required conditions of temperature, concentration and atomising air pressure. It was necessary to determine the addition rate of granulating solution for each particular set of run conditions since this was dependent upon concentration, viscosity, temperature and spray nozzle set-up.

At the end of the spraying phase the supply of atomising air was switched off, together with the compressed air used to force the granulating solution into the nozzle. The residual air pressure was then released. The fluidising air temperature and volumetric rate were increased immediately to 65°C and 30 x 10^{-3} $m^3 s^{-1}$ respectively since this provided the optimum drying conditions for the wet granules. Drying proceeded until a predetermined bowl temperature was reached when the process was terminated. The amount of moisture within a granule can significantly affect the physical properties of that granulation. For comparative purposes it is essential to dry each batch of granules to a specific moisture content. In this work the bowl temperature was used as the drying end point, previously found by experimentation, since the dried granulations were of equivalent moisture content. This ensured the elimination of error when assessing granule and tablet properties.

After drying, the mechanical shaking device was activated and the granules stored.

2.3 STANDARD TEST METHODS FOR SOLUTIONS

2.3.1 Du Nuoy Tensiometer

The surface tension of liquids was measured using a Du Nuoy Tensiometer. This instrument measures the force required to detach a platinum wire ring from the surface of the test liquid. This force is applied by means of a torsion wire attached to a scale calibrated

directly in units of surface tension. A description of the instrument and mode of operation has been described by Richards (1972).

The value of surface tension for each liquid used in the calculations was the mean of five determinations. Determinations were measured at a constant temperature of 20°C.

2.3.2 Weight per Millilitre (Density)

The weight per millilitre for an individual liquid was measured using the method as described in the British Pharmacopoeia 1980 (A76). The value for each liquid used in the calculation was the mean of five determinations. A constant temperature of 20°C was maintained during all measurements.

2.4 TEST METHODS FOR GRANULES

The measurement of certain granular properties is important since they influence the production of uniform tablets. Changes in granule size (Arambulo et al, 1953) and particle size distribution have been shown to affect tablet weight variation. The latter also exerts a marked influence upon tablet crushing strength (Raff et al, 1955) and content uniformity of the compressed tablet (Brochmann-Hanssen, 1963). It has been demonstrated that specific surface, shape, hardness, surface characteristics and size can profoundly influence dissolution rates of drugs from solid dosage forms (Wagner, 1961; Nelson et al, 1964; Lazarus et al, 1964 and Levy et al, 1963). Therefore a knowledge of the physical properties of granules is essential in order to assess a particular process or item of equipment.

Of the granule tests available, several simple standard tests were selected and subsequently performed on each set of granules produced in the fluidised bed granulator.

2.4.1 Size Distribution

In the preparation of pharmaceuticals, the size of particles and their distribution are very important. There are many methods of size analysis which can be used for pharmaceutical granules. These include microscopic methods, sedimentation methods, elutriation methods, centrifugal methods and screening or sieving.

Screening or sieving, is the most common method of particle size analysis for granules, and was used in this work since the equipment, analytical procedure and basic concepts are simple.

Sieve Analysis Procedure

The particle size distribution and mean particle size by weight were determined by sieve analysis, using the ISO series of British Standard sieves (B.S. 410, 1976). Eleven B.S. test sieves (Endecott Ltd.) were placed in ascending order with respect to screen aperture. Approximately 100 grams of each batch of granule was placed on the top sieve and the sieves shaken at 3Hz on an Inclyno sieve shaker. The sampling procedure to obtain a 100g representative sample was to place the batch of granules in a polythene bag, thoroughly mix it then remove five 20 gram samples, taken from different parts of the batch. These samples were subsequently remixed prior to the sieve analysis.

At the conclusion of the mixing period the top sieve was removed, inverted over a sheet of white demy paper and carefully brushed to remove all oversize particles (B.S. 1796, 1976). The granules were weighed and the procedure repeated for each of the remaining sieves. For each batch the weights were converted to percentage retained so that a distribution curve could be constructed and subsequently the mean particle size calculated.

2.4.2 Granule Bulk Density

The density of a loose (uncompacted) mass of powder is a characteristic figure for that powder, it is of great importance for powder storage purposes and for choice of compacting dies. It reflects the type of material, particles size and size distribution as well as the shape of the powder.

Normally two density values are quoted for powders and these are poured density and tap density. The poured density is the volume occupied by a loosely packed mass of powder determined by pouring a known weight of powder into a volumetric cylinder under standard conditions. Tap density refers to the poured density of a powder obtained when the receptacle is tapped or vibrated during loading under specified conditions.

During tapping the powder particles are forced to jump and lose contact with each other for a moment during which there is no inter-particulate friction. The powder particles thus rearrange and tapping results in improved packing conditions. Different authors have proposed various techniques for packing. Newitt and Conway-Jones (1958) used high frequency vibration while Marks and Sciarra (1968) adopted the procedure of manually knocking a graduated cylinder. Although these methods for determining both densities seem somewhat crude they are of great value in powder technology.

2.4.2.a Method of Determining Poured (Bulk) Density

Fifty grams of granule were poured through a standard, short stem 15mm orifice diameter glass funnel into a 100ml graduated cylinder. The volume occupied by the granule was read to the nearest 0.5ml and the poured (bulk) density calculated in g ml^{-1}.

2.4.2.b Method of Determining Tap Density

A mechanical jolting volumeter similar to that of Neumann (1953) was designed and built (Fig. 2.5). The cylinder containing granules prepared as for the poured (bulk) density determinations, was carefully placed in a cylinder harness. This was then placed inside the perspex guide and supported by a specially cut cam rotated by a Citenco motor (Citenco Limited) at 120 revolutions per minute. During each rotation the cylinder and harness were raised gradually and then allowed to drop exactly 15mm under its own weight. The granule volume was read at the 20, 100, 250 and 500th revolution. An earlier experiment had shown that after 500 revolutions no further reduction in volume took place. Tap density was calculated in g ml^{-1}.

2.4.2.c Hausner Ratio

Hausner (1967) found that the poured and tap densities of various metal powders depended upon a number of characteristics such as particle size, size distribution, shape and specific surface, all of which together determine the friction conditions within the powders. He concluded that the ratio of tap to poured (bulk) density reflected the friction conditions between particles within the mass of powder

and was therefore of value in predicting powder behaviour during processing.

$$H.R. = \frac{\rho_t}{\rho_p}$$

H.R. = Hausner Ratio
ρ_p = Poured Density
ρ_t = Tap Density

Grey and Beddow (1968/69) measured this ratio and attempted to correlate it with the angle of repose and with flow time using various copper powders. They confirmed that the Hausner Ratio was a useful characteristic of a powder and found a relationship between it and the angle of repose for three differently shaped copper powders although the shape variation of these powders was somewhat limited. Later Riley and Mann (1972), using differently shaped glass particles, reaffirmed that both the angle of repose and the Hausner Ratio increased with increasing departure from the spherical, although the relationship becomes unpredictable at extreme particle shapes possibly due to anomalous packing behaviour.
A large Hausner Ratio value for a powder indicates poor flow due to a high internal friction

2.4.3 Angle of Repose

An intrinsic property of any powder is its resistance to differential movement between particles when subjected to external forces. This property has been described as interparticulate friction and practical methods of assessing this are based on the angle of repose of a loose mass. In general when a powder is poured freely onto a plane surface it forms a cone that has a constant angle between the surface of the pile and the horizontal plane.

A granulation to be compressed must flow easily and uniformly through the tablet machine to produce tablets of uniform weight and the angle of repose permits evaluation of the granulation before compression is attempted: a small angle of repose indicates a granulation with good flow.

Determination of Angle of Repose

An angle of repose apparatus based on the design of Pilpel (1965) was built (Fig. 2.6). It offered the advantage of eliminating cone distortion since the cone is built on a base of fixed radius.

Fig. 2.5 Mechanical Jolting Volumeter

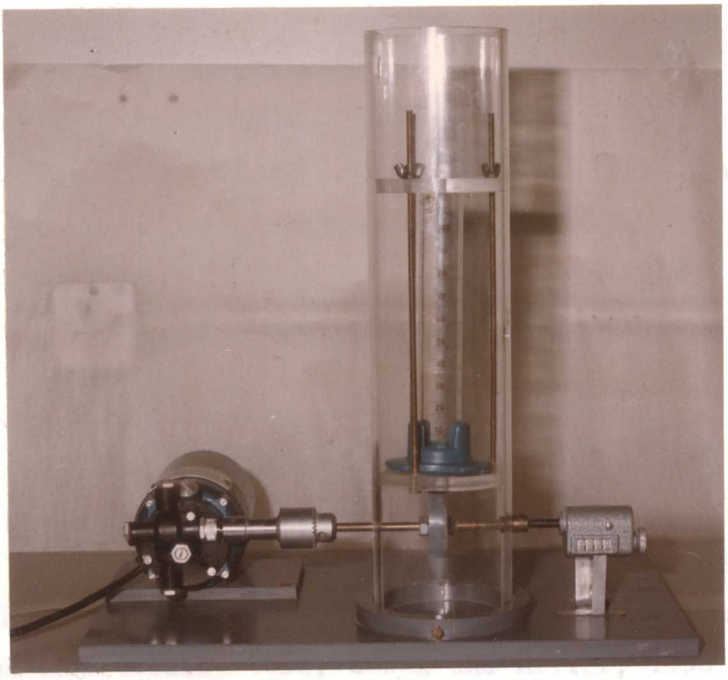


Fig 2.6 Angle of Repose Apparatus

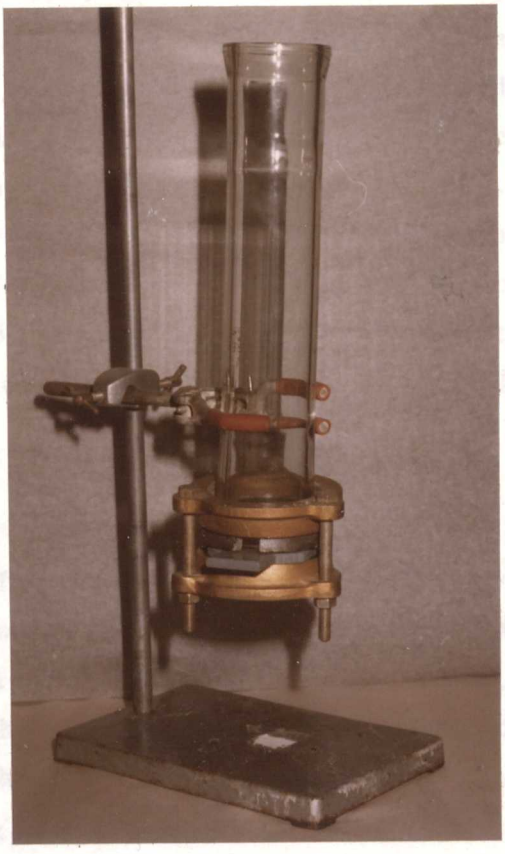


Fig 2.7. Flowometer for rate of granule discharge

The granulation was initially poured into the perspex container (having an in built 75mm diameter horizontal platform). The stopper was removed from the base and the granule allowed to flow out leaving an undisturbed conical heap on the platform. The height of the cone was measured using a cathetometer (Precision Tools and Instruments Limited). For each granulation five determinations were performed and the angle of repose calculated as an average of these using:-

$$\text{Angle of Repose } \theta = \tan \frac{h}{r}$$

h = height of cone

r = radius of platform

2.4.4 Flow Rate

The two most commonly reported physical tests on granules to assess flow properties are angle of repose and flow through an orifice. In many early literature reports dealing with flow of solid materials, angle of repose measurements were used with assumed correlation to flow (Craik, 1958; Craik and Miller, 1958 and Pilpel, 1964). Gold et al (1966a) have shown that in fact there is only a weak correlation in specified systems, which was confirmed by the reports of Jones and Pilpel (1966a and 1966b). In general if the angle of repose is less than 40° then material flows from hopper and orifice with ease. This is extremely important pharmaceutically since uniform die fill is required for high speed rotary tablet machines. Several authors have formulated quantitative relations between angles of repose and flow rates although Carstensen (1973) states that their general validity is questionable. Since the angle of repose is not a reliable method alone to solely evaluate flow properties both tests were performed on each granulation.

Flow through an orifice

The basic method of assessing flow is by the timed delivery of powder through an orifice. Flowometers of more sophisticated design have been described in the literature (e.g. Gold et al, 1966b). Numerous equations (e.g. Bingham and Wikoff, 1931; Newton et al, 1945; Brown and Richards, 1959) have been published to predict flow through circular orifices using a large number of different materials to cover a range of particle sizes. Jones and Pilpel

(1966c) produced the most comprehensive treatment of the parameters involved in flow and derived a general equation to predict flow which is applicable to single and multicomponent materials in a size range of 3 to 300 μm.

Flow rate of powder is an important parameter to measure since it reflects a powder's particle size, particle size distribution, particle shape and its surface characteristics (Crosby, 1960).

Method of Determining Flow Rate

Granule flowability was measured by rate of discharge through an orifice. This was achieved using a glass cylinder (50mm diameter, 350mm length) supported in a vertical position by a clamp stand (Fig. 2.7). Plates of various orifice size could be inserted at the lower end of the cylinder. The cylinder was filled with granules and these were allowed to pass through the orifice in the plate. The discharging granules were collected for a timed period.

Two flow determinations were carried out:

(i) through a 12mm diameter orifice

(ii) through a series of orifices to determine the smallest sized orifice through which the granule would discharge. The rate through this orifice was determined.

All reported flow rates are the average of five determinations. Granules exceeding 2,000 μm were removed from the granulation prior to the flowability determinations in order to prevent blockage of the orifice.

2.4.5 Torque Measurement

The rheological properties of powders and granular masses have been investigated using various rotational viscometers (Benarie, 1961; Taneya, 1963; Kuno and Senna, 1967; Harwood and Pilpel, 1968). These viscometers consist of double cylinders of various design (e.g. baffled) with a torque reading generated by either the force exerted on the inner cylinder by the rotation of the outer or the force exerted on the outer cylinder by the rotation of the inner.

The degree of torque fluctuation exhibited in these systems has been shown to be characteristic of the granular mass (Taneya, 1963). The pattern of these fluctuations belongs to either two types of flow or a mixture of both: Particle flow in which every powder particle moves independently or Block flow in which the powder particles agglomerate in block owing to the cohesion.

Kuno and Kurihara (1964) confirmed these findings indicating that irregularities in powder density caused the oscillations in torque. A final torque value is eventually reached and Taneya (1965) has shown that this can be used to calculate a coefficient of internal friction (intergranular cohesion) of that mass. Harwood and Pilpel (1968)

> demonstrated that torque reading reflected particle size, and flow rate. They also used the measurement of torque to examine the effect of the addition of glidant on cohesive powders.

The shaft torque produced by the movement of a simple paddle blade through a granule mass has also been shown to be indicative of the physical properties of that mass (Weighardt, 1952; Iiyama and Aoki 1960; Novosad and Standart 1965; Bagster and Bridgwater 1967). The types of granular material studied included various shapes and sizes of sand, glass Ballottini beads, polythene chips and sugar.

It was thought that similar torque measurements could be used to characterise the granule batches produced from the 2^7 factorial design. The torque arm mixer as described by Travers, Rogerson and Jones (1975) was slightly modified so that it could be used to measure the shaft torque of a paddle within a granule mass when:-

a) the paddle alone was revolving
b) the bowl was revolving
c) the bowl and paddle were counter rotating

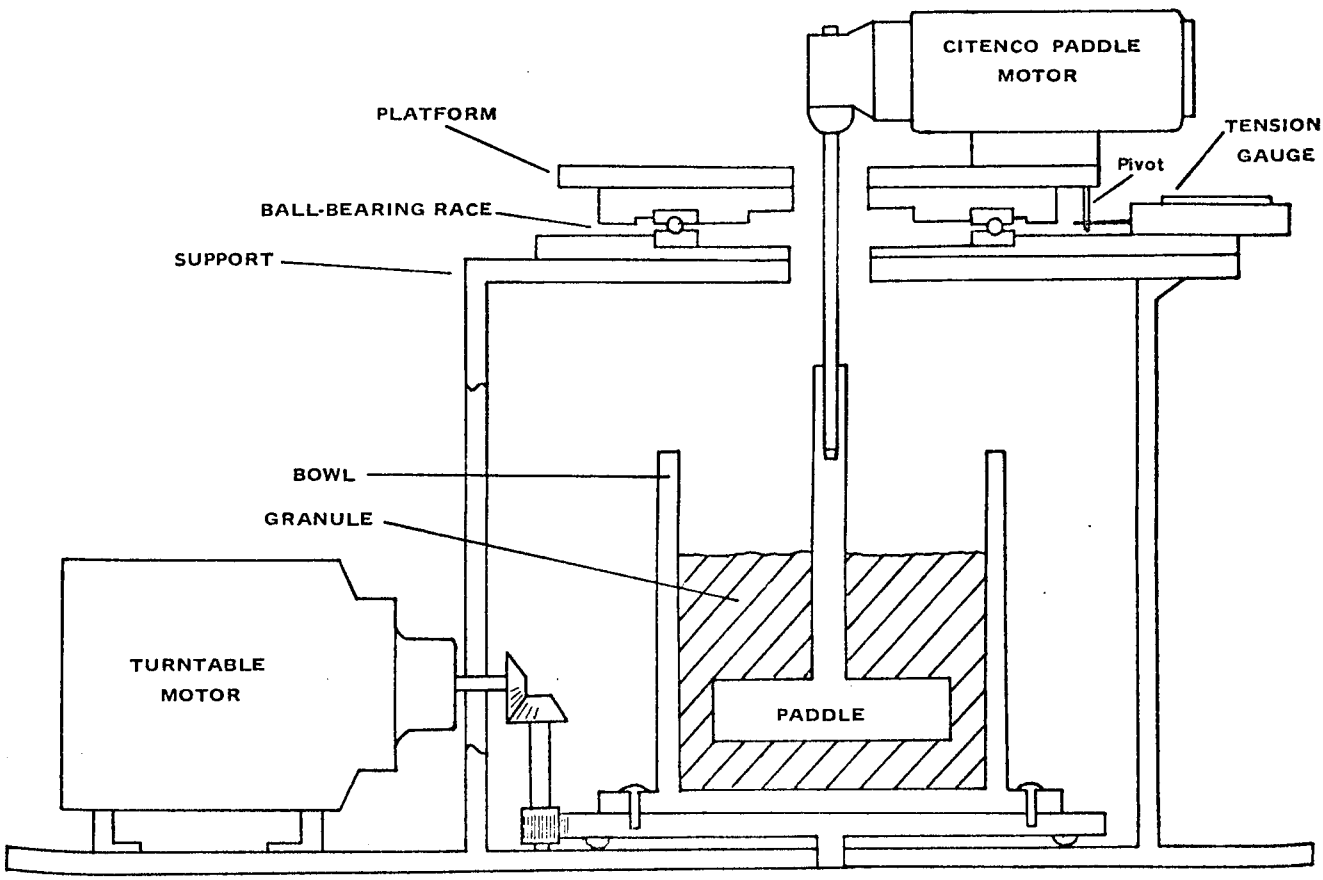
The torque generated could then be compared with the results of the conventional granule tests reported in Appendix III.

(i) Torque Arm Mixer

The apparatus consisted of a modification of the torque arm mixer described by Travers et al (1975). The original bowl was replaced by a small perspex bowl and the mixer arm redesigned with a paddle as indicated in the diagram of the apparatus in Fig. 2.8. The equipment design allowed the mixer arm or bowl to be rotated at various speeds

individually or together in counter rotation. In all cases the torque developed on the mixer arm was measured directly from the gauge after reaching equilibrium.
The small perspex bowl was 145 mm in diameter and 140 mm deep. The paddle consists of a flat face rectangular blade with dimensions 25mm and 115mm, centrally mounted 10mm above the bowl base.

Fig 2.8 Torque Arm Mixer



2.5 BINDER TRACING TECHNIQUES FOR GRANULES

2.5.1 Fluorescent Tracing

The basis of fluorescent tracing depends upon a molecule (fluorochrome) absorbing a quantum of radiation of sufficient energy that it attains an excited state with a different electronic distribution. The molecule then returns to its initial state by emitting radiation. This phenomenon is termed fluorescence and is almost always of longer wavelength than the exciting radiation. The energy changes associated with this are usually explained by reference to the potential energy of a simple diatomic molecule as a function of nuclear separation (Nairn, 1969).

The nature of the environment can have a tremendous effect upon the level of the fluorescence. Changes in pH, viscosity, temperature etc. can exert a significant variation on the degree of fluorescence.

Criteria for judging a fluorochrome as a suitable fluorescent label in immunology have been defined by Chadwick et al (1958) and later amplified by Pearse (1968) as:-

(a) the fluorochrome should possess chemical groups which will form stable covalent bonds with protein molecules or be easily convertible to such a reactive form without destroying the fluorescent nature. Easy removal of any unreacted fluorescent material is also important.

(b) the fluorescence efficiency of the dye must be high and should decrease as little as possible on conjugation to the protein.

(c) the fluorescent colour of the conjugate should be different from that of the background tissue.

(d) the conjugate should be stable under normal storage conditions and not differ materially in its properties from the unconjugated protein.

(e) the conjugation procedure should be as simple and as short as possible.

These criteria for fluorochromes are as relevant to immunological tracing as they are for their proposed use in the investigation of the granulation mechanism by monitoring the role of the binder.

2.5.1.a Binder/Fluorochrome Conjugation

Although there are a large number of fluorochromes available only a few have proved satisfactory tracers. Fluoroscein isothiocyanate (FITC) and Lissamine Rhodamine B (RB 200) are generally regarded as being the tracers of preference.

For the proposed study FITC was considered as the fluorochrome of choice since it:-

a) is stable and can be stored in darkness for long periods without loss of activity.

b) gives an immediate, intense green fluorescence.

c) requires low ratios of fluorochrome to target material. Therefore adequate fluorescence is obtained with low levels of conjugation.

Labelling of proteins with FITC involves an electrophilic attack by the FITC upon the α-amino group of lycine (Nairn, 1969). The proposed binder to be conjugated with FITC is PVP. Since the nitrogen atom of the pyrrolidone rings of PVP is weakly basic, the FITC will form a link with this heterocyclic nitrogen atom and thus be bound, possibly as a complex to the PVP (see Fig. 2.9). Confirmation of this reaction can be obtained from the cycloaddition of Phthallic anhydride with isocyanate (Hurd and Papas, 1959; Otves, Marton and Agoston, 1960) as shown in Fig. 2.10. It is believed that the conjugation of the FITC to the PVP is supported by this reaction.

2.5.1.b Conjugation Process

To bind the FITC to the PVP, the method of Rinderknecht (1962) was adopted. A carbonate-bicarbonate buffer (pH 9.0, 0.5M) was prepared by dissolving 3.7 g of sodium bicarbonate and 0.6 g sodium carbonate (anhydrous) in sufficient double distilled water to make 100 ml of solution. To this solution 5 mg of FITC was added. The conjugate

Fig. 2.9. 'Possible' reaction mechanism for synthesis of PVP/FITC conjugate

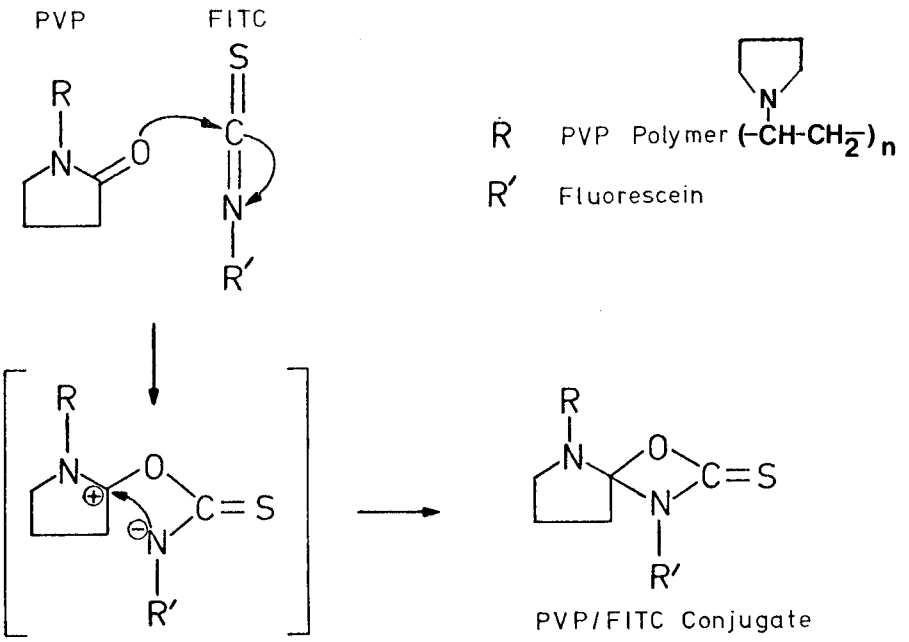
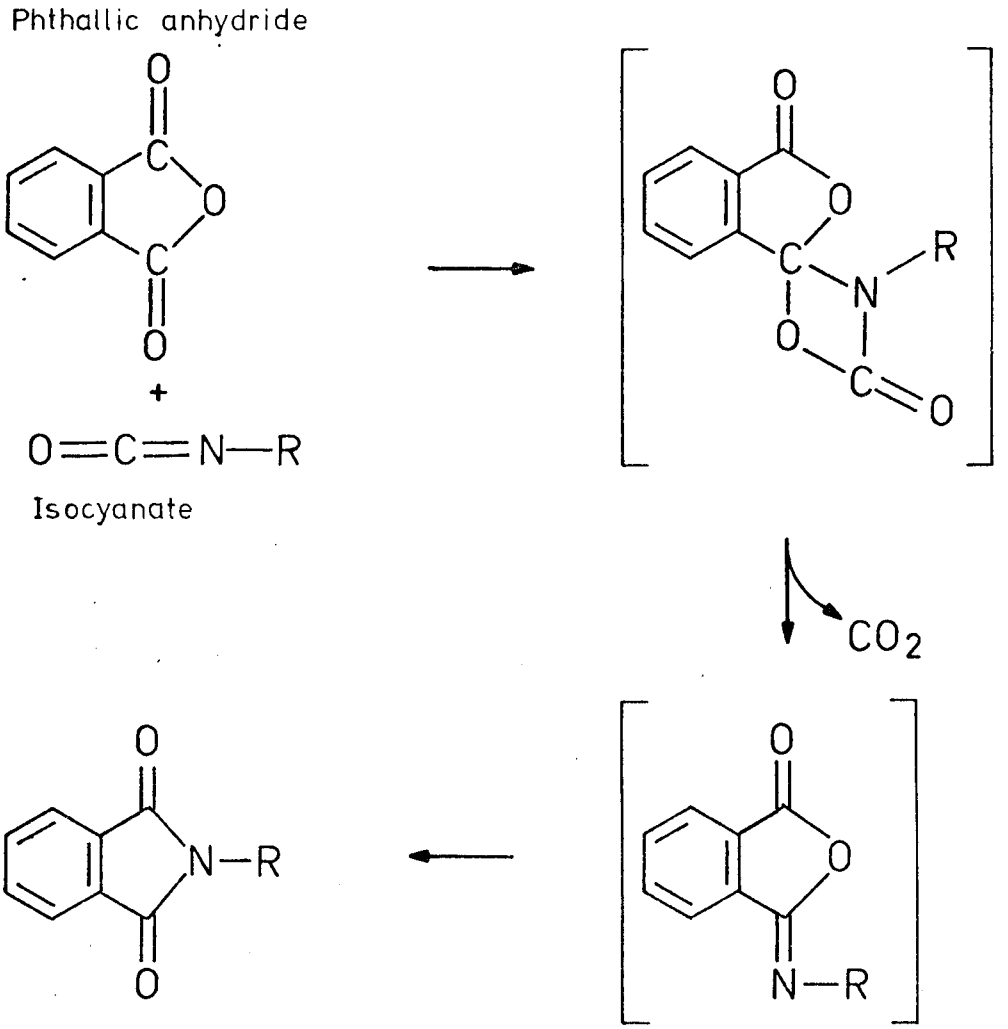


Fig. 2.10 Cycloaddition of Phthallic anhydride with isocyanate



was then prepared by adding 50 ml of this fluorescent buffer solution slowly and with constant stirring to 50 ml of 10% $^{w}/_{v}$ PVP solution. Finally to allow complete conjugation to occur this solution was shaken for 24 hours.

For good conjugation it is essential that there is efficient stirring, slow and gradual addition of the FITC buffer solution and a maintenance of an alkaline pH. The maintenance of the alkaline pH is achieved by the high buffering capacity of the system.

2.5.1.c Conjugate Purification

When conjugation was complete, after 24 hours agitation, the reaction mixture contained unreacted fluorescent material (UFM). It was essential that this should be removed in order to avoid non-specific fluorescence which would not indicate the true presence and thus distribution of the PVP. A suitable separation method is that of gel filtration or gel chromatography. The technique is based upon the diffusion of small molecules into the pores of a gel from which large molecules are excluded because of their size. Sephadex (Pharmacia, Uppsala, Sweden) is such a chromatographic material made of cross linked dextran. Various types of Sephadex are available, differing in their swelling properties. This being an important characteristic of the gel.

The separation procedure was achieved by a column technique with molecules larger than the largest pores of the swollen Sephadex, unable to penetrate the gel particles and therefore passing through the bed in the liquid phase outside the particles. These molecules are eluted first; in this case the FITC/PVP conjugate. Smaller molecules (e.g. free unattached FITC) however penetrate the gel particles to a varying extent depending on their size and shape. Molecules are therefore eluted from a Sephadex bed in order of decreasing molecular size.

The choice of the appropriate Sephadex type depends upon the molecular size and the chemical properties of the substances to be separated. Rinderknecht (1962) however recommended the use of grade G-25, which gave good separation for fluorescent proteins.

Sephadex Separation

Column Preparation

To obtain satisfactory flow rates and good separation with the gel, it must be carefully prepared. The required quantity of dry Sephadex, as indicated by the Pharmacia Literature, sufficient for a 26 mm internal diameter and 600 mm high column, was placed in a suitable glass flask filled with water. This was heated on a water bath for 6 hours to accelerate swelling. The final gel slurry was deaerated by vacuum before packing the column.

Correct packing of the column is extremely important since irregularities give rise to uneven flow resulting in zone broadening. The column was mounted vertically, half filled with water and the previously swollen slurry, of sufficient quantity for the experiment, poured carefully in. The gel was allowed to settle and washed with several column volumes of phosphate buffer (0.02 M, pH 6.5) at the recommended flow rate (Pharmacia Literature).

Before beginning conjugate separation, the homogeneity of the bed was checked by running through 2 ml of a 50/50 Dextran Blue/Dichromate (2 mg/ml) mix. Observation of the dye zones progressing down the column indicated the degree of dye separation and quality of gel packing.

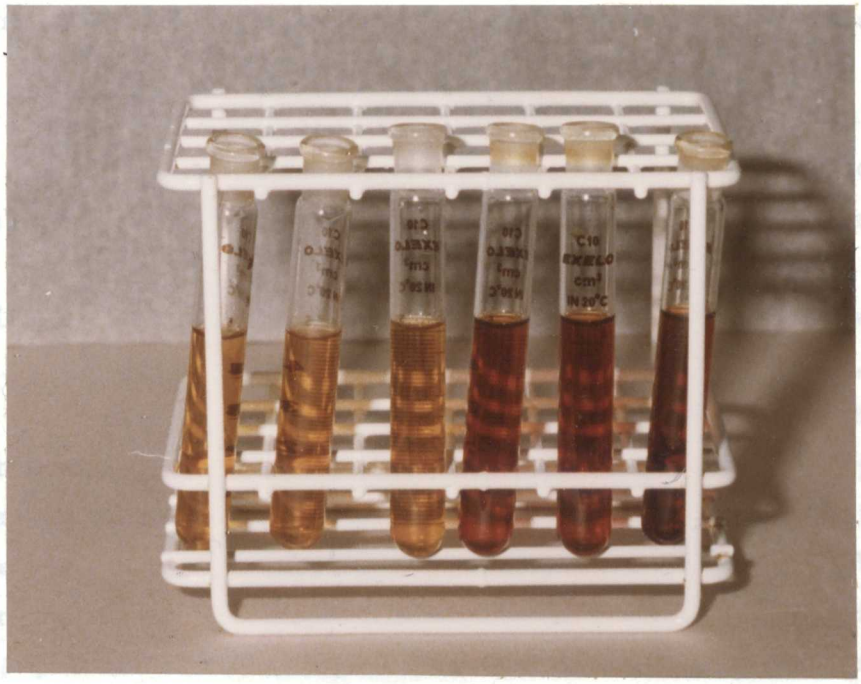
Separation

The use of G-25 Sephadex gel has been recommended (Nairn, 1969) for separation of fluorescent dyes from conjugate mixes. This gel offers the advantage of good flow rates with fast separation. Such a column was prepared and an initial load of 5 ml of conjugate mix, developed with sodium phosphate buffer, failed to give two separate zones of dye. Further attempts at separating 5 ml aliquots gave similar results.

Another grade, G-75, with a larger water regain volume, giving greater resolution was used. A column was prepared as indicated in the previous section. Initial runs with 5 ml conjugate mix aliquots, developed with sodium phosphate buffer at a flow rate of 0.35 ml/min, gave extremely good separation. This was indicated by two distinct bands of fluorescence slowly progressing down the column.

An automatic sampler collected eluate from the column at 23 minute intervals. The volume of each sample after 23 minutes was 8.0 ml. The separation volume i.e. the volume which separates the front of the elution curve of the conjugate mix from that of the unattached FITC at the flow rate of 0.35 ml/min was 255 ml. Theoretically the maximum sample size that the column could process is equivalent to this volume. However zone broadening did take place and it was considered that a sample size of 50 ml conjugate mix would be the maximum permissable volume. This broadening was also attributed to the bed basket at the top of the column acting as a partial filter and retaining a small portion of the conjugate mix. The problem was partially alleviated by removal of the bed basket and carefully applying the conjugate mix directly to the gel surface to give a uniform front with minimal bed disturbance. The position of the PVP-FITC conjugate was confirmed as being the first fluorescent band collected from the column by using the Pharmaceutical Codex (eleventh edition, 1979), identification test for PVP. Exactly 5 ml of liquid was removed from successive collected samples and 0.2 ml of 0.1 N iodine added to each. The presence of PVP was confirmed by a deep red colour being immediately produced as indicated in Fig 2.11.

Fig. 2.11. Red colouration produced by addition of 0.1N iodine, indicating the presence of PVP in eluate (Pharmaceutical Codex identification test).



However when a 50 ml volume of conjugate mix was processed down the column poor separation with no definition between the conjugate and the unattached FITC occurred. This was considered due to the adhesive properties displayed by the PVP, thus slowing the progression of the PVP-FITC zone down the column.

The sample size was subsequently reduced to 20 ml. Good separation occurred. This was confirmed by once again testing each sample collected with the PC test for PVP. The intensity of the colouration for each sample was subsequently measured using an Evans Colorimeter (Evans Electroselenium Ltd., Halstead, Essex) fitted with a green 404 nm filter. The results are displayed graphically in Fig. 2.12. It is clearly shown that the bulk of the PVP-FITC conjugate is recovered in the region of the void volume (samples 9 - 18) whilst the uncombined FITC was recovered in the region of the total fluid volume of the column (samples 39 - 50). The position of the unattached FITC was obtained by subjective viewing of the samples for fluorescence. It should be noted that the colorimeter readings are not quantitative although an approximate estimation of PVP concentration can be obtained.

2.5.1.d Determination of PVP Concentration in Samples collected.

The G-75 column was developed with a 20 ml sample of 0.02M sodium phosphate buffer (pH 6.5) containing 5% w/v PVP. Samples of eluate were collected at 23 minute intervals as previously described.

Each sample was subjected to the PC identification test for PVP with the colouration measured colorimetrically as previously described. The position of the PVP and intensity of the colouration were identical to those obtained from the PVP-FITC conjugate determination.

A linear relationship was found between the concentration of PVP in 0.02M sodium phosphate buffer and refractive index. This enabled a calibration curve to be constructed (Appendix I) which was used to obtain a reasonably accurate estimation of the quantity of PVP in the samples (aliquots 9 - 18) collected from the column. Refractive index from each of these samples are shown in Table 2.3. Subsequent calculation from these readings showed that 90% of PVP added to the column was present within samples 9 - 18. The overall concentration of PVP in this 80 ml volume was approximately 1% w/v.

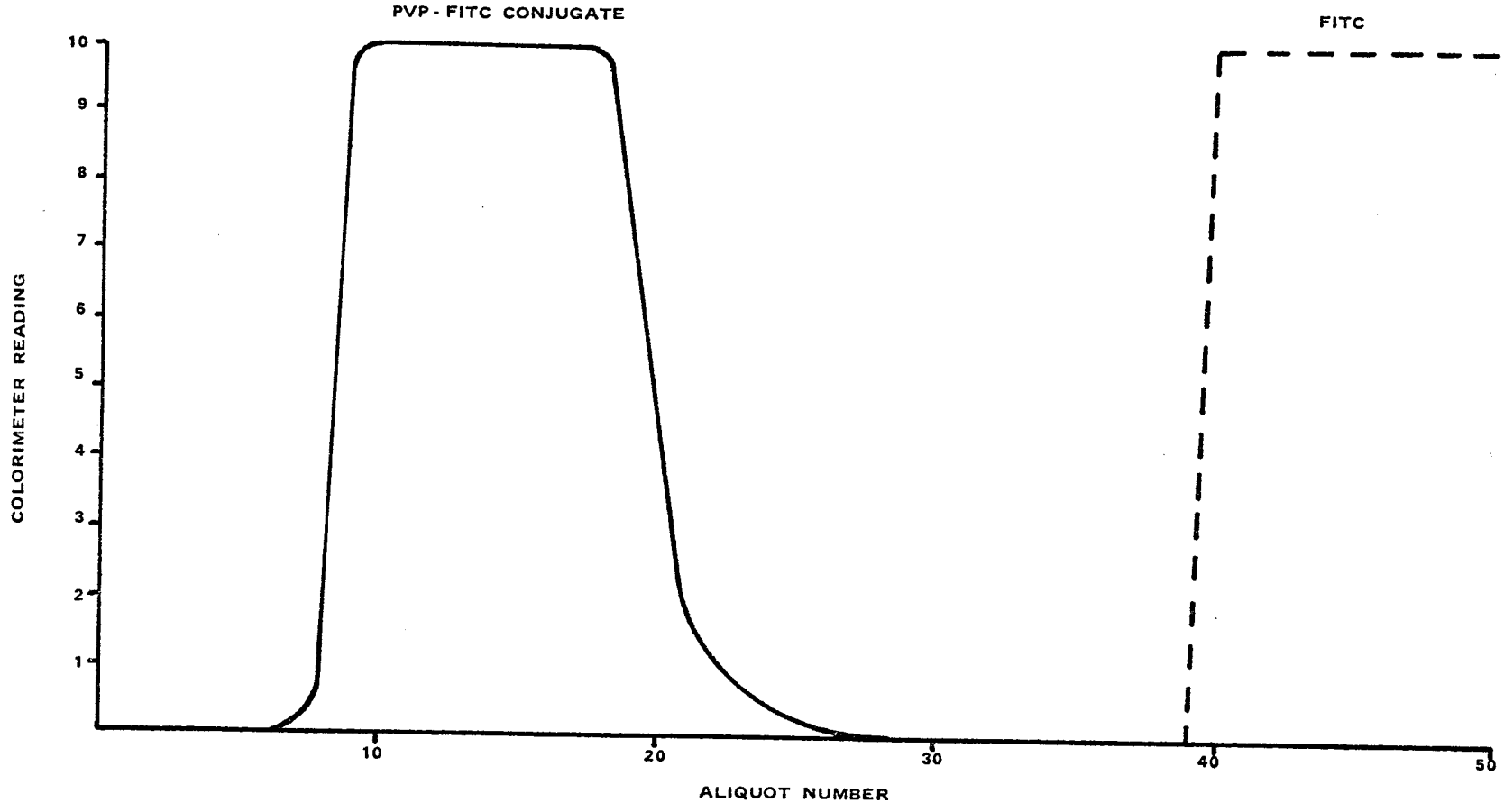


Fig. 2.12 Colorimeter Reading against Aliquot Number

(after subjecting samples to the PC identification test for PVP)

Table 2.3 Refractive Index measurements from each 8 ml aliquot taken from Sephadex column. This is used to calculate concentration of PVP in solution.

Aliquot No.	Refractive Index	Estimated amount (mg) of PVP in aliquot
9	1.3349	40
10	1.3358	88
11	1.3362	104
12	1.3369	136
13	1.3366	120
14	1.3362	104
15	1.3360	96
16	1.3358	88
17	1.3350	40
18	1.3350	40

$$\% \text{ PVP present (in aliquots 9 - 18)} = \frac{\text{Total weight in aliquots}}{\text{Total weight PVP added to column}} \times 100 = \frac{896}{1000} \times 100$$

$$\% \text{ PVP} = \text{Approx. } 90$$

2.5.1.e Ultrafiltration as a method of conjugate purification.

The purification of the conjugate mix using Sephadex separation is an extremely lengthy process (24 hours per run). Although this technique does offer the advantage of excellent separation only a

20 ml charge of mix can be processed at any one time. The use of ultrafiltration as a possible alternative method was considered. Ultrafiltration has been used in biological sciences to quickly and efficiently separate large volumes. It was thought that the small pores of the filter membrane would only allow the smaller unattached FITC molecules to pass through. Initial trials using a UM 10 filter proved unsuccessful since the filtrate gave a positive result when tested for presence of PVP. A finer pore sized filter, UM 02 was tested. This again proved unsuccessful since PVP was detected in the filtrate, only slow filtration rates were obtained and the PVP-FITC conjugate formed a deposit on the filter surface thus reducing the filtration rate.

The results from these feasibility studies therefore eliminated ultrafiltration as a possible alternative to Sephadex separation. It was concluded that the only efficient method of separating the conjugate mix was by using a Sephadex G-75 column.

2.5.1.f Application

During wet granulation PVP is generally used in concentration of not less than 5% w/v. The final concentration of conjugate from the column of only 1% w/v was therefore adjudged as being too dilute. Concentration of this solution was essential and was achieved by freeze drying. It was considered that this method would not adversely affect the chemical conjugation between the PVP and FITC molecule.

Preparation of Freeze Dried PVP-FITC Conjugate.

The dilute, purified conjugate mix, removed from the column was freeze-dried using a laboratory scale Chemlab Model SB6 freeze dryer. Approximately 40 ml aliquots of conjugate mix were placed in round bottomed flasks. Each one was partially immersed in liquid nitrogen and continuously revolved until the mix had frozen to a thin layer covering the inside of the flask. Immediately each flask was transferred to the freeze dryer and placed under vacuum. At the end of the drying process the solid PVP-FITC conjugate was removed and stored in tightly sealed glass containers. All diluted conjugate mixes recovered from the column were processed in this manner and stored until reconstituted with water for use in the investigation into the granulation mechanism within the processor. The conjugate readily dissolved in water during reconstitution to give a fluorescent solution with PVP binding properties.

2.5.1.g Fluorescent Microscopy

All samples containing the fluorescent PVP-FITC conjugate were observed by an incident light fluorescence technique employing a Vickers fluorescence microscope (M41 Photoplan).

The principle of incident light fluorescence lies in illuminating the specimen on the slide from above by using an interference mirror filter with a high reflectance for the wavelengths of the primary irradiation, ultraviolet light. The mirror filter is designed to permit high transmission of the longer wavelengths of the fluorescence emission from the specimen which is viewed through the filter. A diagrammatic representation of the system used in the Vickers M41 photoplan is shown in Fig 2.13. High pressure mercury light passes through a 475 nm suppression filter and a FITC exciter filter (the peak absorption of FITC conjugates is at 495 nm) then via a FITC dichroic mirror filter and a fluorite objective to the sample. The emitted fluorescence passes back through the objective and the dichroic, then via a 515 nm barrier filter to the eye piece (peak emission for FITC conjugates is 520 nm). A camera system enabled permanent records to be made. These photographic records were taken utilising an automatic exposure unit to give low exposure times and Ektachrome-X film (ASA 64 'Kodak') to give good colour reproduction.

2.5.2 Solvent Extraction Procedure

The basic principle behind this technique relies upon the ability to dissolve all the constituents, except the binder, from a granule without damaging the integrity of the original structure. This enables the remaining matrix to be studied since the binder distribution and structure can be easily identified. Seager et al (1979) used this technique during their comparative studies with granules consisting of paracetamol, magnesium stearate and gelatin prepared by roller compaction, conventional wet massing and spray drying.

Fortunately in this study the selection of salicylic acid granulated with PVP enables the solvent extraction procedure to be easily performed. Salicylic acid being readily soluble in ether whilst the PVP is insoluble. Magnesium dried diethyl ether BP was used in all extraction procedures.

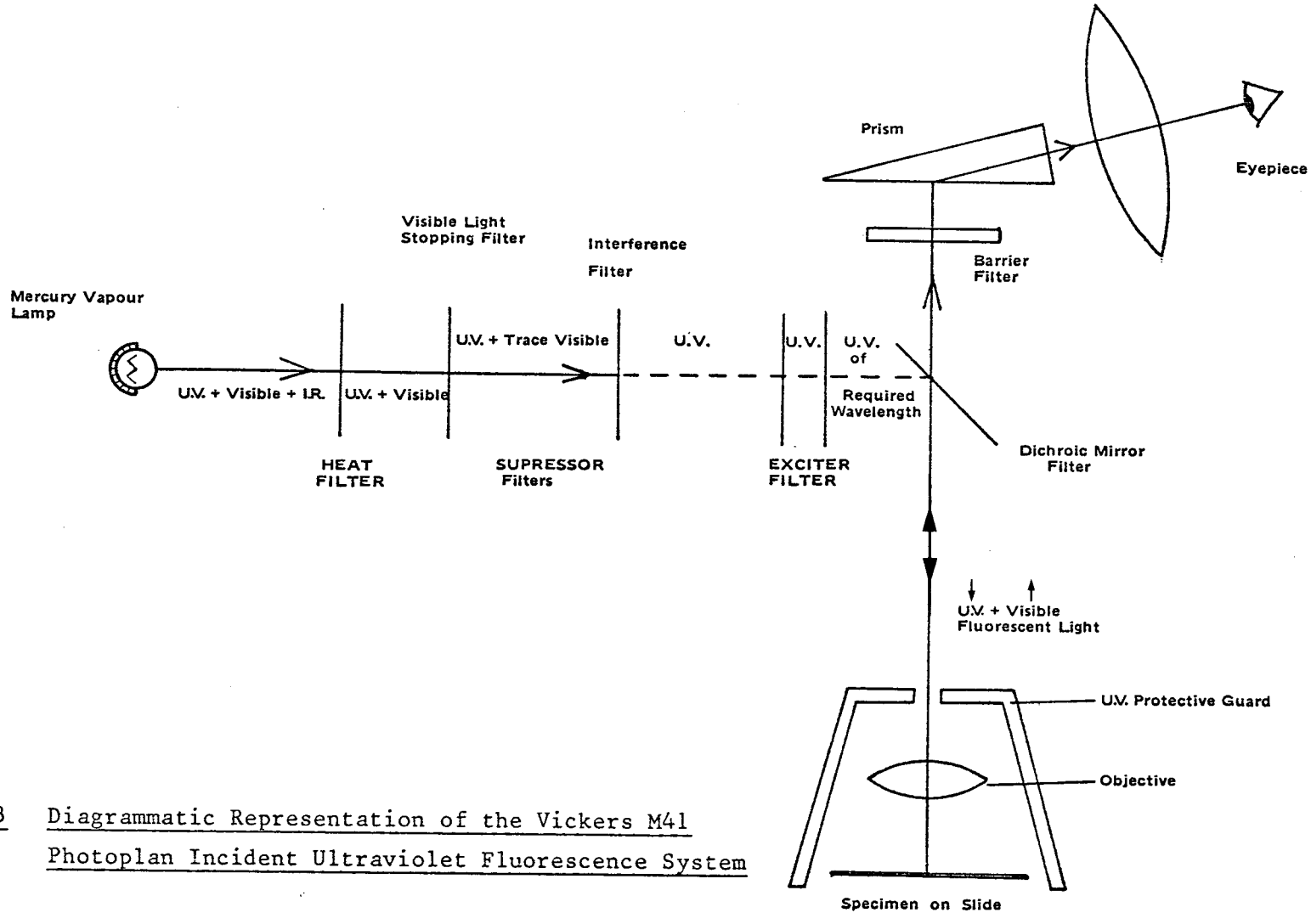


Fig. 2.13 Diagrammatic Representation of the Vickers M41 Photoplan Incident Ultraviolet Fluorescence System

Several potential solvent extraction methods were evaluated. These included:-

(a) dropping ether carefully on the end of an inclined microscope slide previously sprinkled with granules. Not all the salicylic acid could easily be removed using this procedure. Salicylic acid recrystallised out on the slide as the ether evaporated during its journey down the slide.

(b) shaking granules with several volumes of ether in a glass separation vessel, finally decanting off the excess ether and pipetting the supernatant suspension onto a SEM stud and allowing the ether to evaporate. The ether greatly affected the adhesive properties of the glue on the microscope stud. Several washings were necessary before completing the salicylic acid extraction.

(c) allowing ether to slowly permeate through a column of granules. The eluate was continuously tested for salicylic acid and immediately this monitoring proved negative the procedure was terminated. Granule packing however, occurred in the column with the majority of the individual residues losing their integrity and the remaining residues suffering damage.

(d) fluidising granules with a continuous stream of ether and after complete extraction allowing ether evaporation to produce a dried residue suitable for direct transfer to a SEM stud.

Of the 4 procedures investigated the latter, employing a fluidised bed system, provided the best results and it was thus used as the method of choice for all the extractions. This method is more fully discussed in section 2.5.2.a.

2.5.2.a Fluidised Bed Extraction

A specially designed glass extraction tube was constructed. This consisted of a main body and a glass filter/distribution grid together with moulded inlet and carry over tubes as diagrammatically illustrated in Fig. 2.14.

Fig. 2.14 Extraction Tube

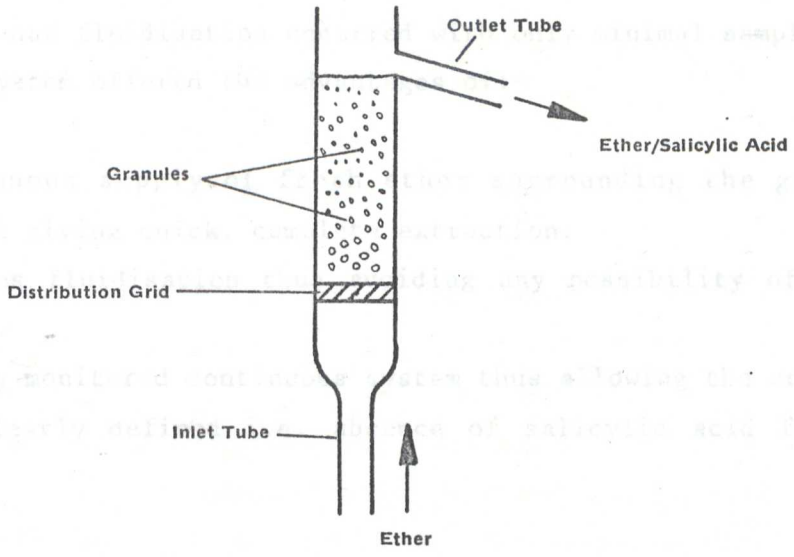
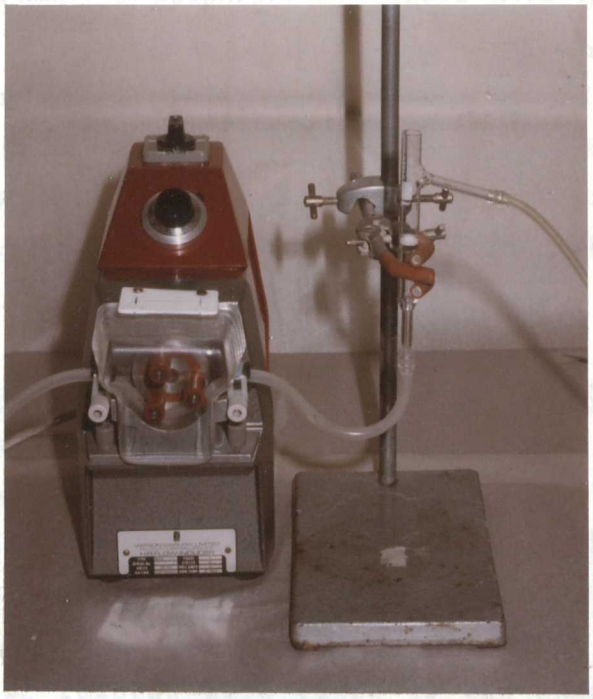


Fig. 2.15 Apparatus for Fluidised Bed Extraction



The apparatus functioned by pumping ether from a reservoir through the inlet tube by means of a variable speed peristaltic pump as shown in Fig. 2.15. When the ether flow rate had stabilised, approximately 0.5 g of granules were added and the flow adjusted to such a value that fluidisation occurred with only minimal sample carry over. This system offered the advantages of:-

(i) a continuous supply of fresh ether surrounding the granules therefore giving quick, complete extraction.
(ii) continuous fluidisation thus avoiding any possibility of agglomeration.
(iii) an easily monitored continuous system thus allowing the end point to be clearly defined i.e. absence of salicylic acid from the eluate.

At the completion of extraction, fluidisation by ether addition was terminated and replaced by air. This aided ether evaporation from the bed with the integrity of the binder residues being maintained by air fluidisation. A dried mass of individual binder residues remained after complete evaporation. These were transferred to the microscope stud by careful inversion of the tube and gentle tapping. The diameter of the tube had exactly the same dimensions as the microscope stud thus loss of material was minimal. Each fluidised bed extraction was so performed using at all times thoroughly cleaned and dried equipment. The residues were viewed using SEM as described in section 2.5.3.

2.5.3 Examination by Scanning Electron Microscopy (SEM)

All samples were mounted on a SEM plinth and coated with gold by a vacuum deposition technique. As the plinth was rotated in a planetary motion 100 mm of 0.2 mm diameter gold wire was evaporated from a tungsten filament positioned 100-150 mm from the sample in a vacuum in excess of 1×10^{-4} torr (0.13 μbar).

Photographic records were taken as the sample was examined using a scanning electron microscope (model CESA, AEI) at 20 kV.

2.6 GRANULE COMPRESSION

Granules were compressed on a Manesty BB3B tableting machine instrumented with strain gauges. Four strain gauges were attached to the eyebolt of the lower compression roller carrier to form a Wheatstone Bridge. This enabled compression force to be measured directly using a Hewlett Packard amplifier (model 8805B) and a U.V. oscillograph thermal writing recorder (Model 7702B). Formulae and operating conditions during compressing are described in sections 3.6.1 and 5.5.1.

2.7 STANDARD TEST METHODS FOR TABLETS

Several methods are employed in determining the physical properties of tablets. Early methods of standardisation were made or omitted at the discretion of the manufacturer. The overall result of this was that many tablets on the market were extremely unsatisfactory. The British Pharmacopoeia (B.P.) 1932, Addendum VII 1945, introduced official standardisation which has resulted in every manufacturer producing tablets with exact characteristics for a batch to batch basis. French et al (1967) compared pharmacopoeial standards and specifications for tablets in six pharmacopoeias and concluded that there are no set of universal standards.

In the U.K. pharmaceutical industry today the B.P. (1980) methods are used as minimum routine quality control standards. In this work these tests and others were used as a basis to assess the physical properties of tablets compressed from the different batches of granules produced. A description of these methods is given as follows.

2.6.1 Crushing Strength

For all measurements of crushing strength several types of apparatus have been developed, among which are the Strong-Cobb, Monsanto, Pfizer and Schleuniger units. These are generally based upon the application of force applied across the diameter of the tablet by a moving platen against a stationary platen. Variability in results can arise from use of such testers (Brook and Marshall, 1968) especially when applying a force manually to the tablet.

In this work the Schleuniger unit (Dr. K.Schleuniger and Company) was used to measure crushing strength since it is mechanically driven; it is easy to use and the tablet under test does not have to be secured in the jaws of the instrument which can be a source of inaccuracy. The Schleuniger tester operates in a horizontal position. A moving anvil presses the tablet against a stationary anvil. As force

is applied to the edge of the tablet, a pendulum swings away from its normal position. Its movement is followed by a pointer moving along a scale. When the tablet breaks, the pendulum swings back to its original position while the pointer indicates the scale reading in kilograms. The crushing strength of ten tablets from each batch was measured.

2.7.2 Thickness

The thickness of a tablet is an important measurement since it is often directly related to tablet crushing strength and therefore is sometimes used as an initial control of this parameter. Thickness can vary with no change in weight due to differences in the density of the granulation and the pressure applied to the tablets as well as the speed of compression. Industry applies tablet thickness specifications to individual products since any significant deviation from this will adversely affect packaging.

The thicknesses of ten tablets from each batch were measured, using a dial micrometer (Mercer) reading to 0.01mm.

2.7.3 Weight Variation

Tablet weight is an important parameter since it is often directly related to the amount of active ingredient within the tablet. Indeed Airth et al (1967) suggested that a tablet weight variation test could be used rather than a content uniformity test, in which the proportion of active ingredient was high. Not only can the weight variation be associated with granule properties it has also been shown to be correlated with compression force (Goodhart et al, 1968) and also compressing machine performance. In tablet production samples are taken at set times and enable any variation to be compensated for. The specific weight variation tolerances can be found in the various pharmacopoeias.

The individual weights of twenty tablets were measured for each batch, on an automatic balance (Oertling) reading to 0.1mg.

2.7.4 Friability

Friction and shock are the forces that most often cause tablets to chip, crack or break during packaging, handling or shipping. In

order to measure the resistance of tablets to such 'wear and tear' several shaking devices have been used (Smith, 1949a; Smith, 1949b; Burlingson and Pickering, 1950; Webster and Van Abbé, 1955). Today, the most generally used method of assessing this parameter is by using the Roche friabilator (Erweka Apparatus Limited) which was first described by Shafer et al (1956). This test not only subjects the tablets to self abrasion but also to a controlled series of falling shocks over a period of time. The tablets can then be reweighed and their loss of weight converted to percent friability.

The Roche friabilator was used to assess the tablets produced in this work. The test procedure was to dust then weigh twenty tablets from a batch and place them in the friabilator which consisted basically of a curved scoop within a plexiglass drum. The scoop interrupts the rotational movement of the tablets and provides falling as well as frictional force to the test sample. After one hours rotation, at a speed of 0.5 Hz, the tablets were removed, dusted and reweighed. The percent friability was then calculated.

2.7.5 Disintegration

Although the disintegration test has been largely superseded by the dissolution test it nevertheless provides useful data for the formulator and a quick, simple test for production control. Many national pharmacopoeias describe tablet disintegration tests although different methods and end points are quoted.

The test used in this work is that described in the B.P. (1973) appendix 13I, using the Manesty tablet disintegration tester Mark III (Manesty Machines Limited). The test basically consists of placing five tablets from a batch into a basket which is then raised and lowered into distilled water at 37°C. The disintegration time is the time between the tablets coming in contact with the water until no tablet debris remains on the gauze. This test was performed twice for each batch.

2.7.6 Dissolution Test

The basic apparatus consisted of a 1 litre beaker with a rotating basket containing one tablet.

(B.P. 1980 Apparatus and Method using a speed of 100 rpm)

Artificial gastric juice was prepared using the formula:

SODIUM CHLORIDE	2 g
CONCENTRATED HYDROCHLORIC ACID	7 ml
DISTILLED WATER	to 1000 ml

Prior to the dissolution test a calibration curve was constructed using a series of salicylic acid solutions in artificial gastric juice up to 0.0003% $^{w}/v$ (Appendix II). The absorbance of each solution was measured at 300 nm.

The speed of the Citenco motor was set at 100 revolutions per minute. One preweighed tablet was placed in the rotating basket which was subsequently attached to the stirrer motor. This was introduced into the empty dissolution vessel which was immersed in a water bath at 37°C. The stirrer motor was switched on and one litre of artificial gastric juice, prewarmed at 37°C, poured into the dissolution vessel. Immediately a stop clock was started and 5ml of sample removed from the dissolution vessel after 5 minutes. This sample was filtered through a Millipore filter unit (pore size 0.45 μm) and assayed for salicylic acid at a wavelength of 300 nm using artificial gastric juice as a blank. A 5 ml aliquot of fresh artificial gastric juice was added for each 5 ml sample withdrawn from the dissolution vessel. Further samples after 10, 15, 20, 30, 45, 60, 90, 120 minutes were removed using an identical procedure and sampling position. Each sample was assayed for salicylic acid content.

CHAPTER 3

INVESTIGATION INTO THE INFLUENCE OF PROCESS VARIABLES UPON GRANULE QUALITY

CHAPTER 3

INVESTIGATION INTO THE INFLUENCE OF PROCESS VARIABLES UPON GRANULE QUALITY

3.1 INTRODUCTION AND SCOPE OF CHAPTER

In the early 1960's the introduction of the process of fluidised bed granulation seemed, initially, to be a major breakthrough in granulation technique. It enabled the three stages of granulation, namely mixing, wet massing and drying to be achieved in a single plant item. From an industrial viewpoint the method was potentially useful since it could increase productivity, reduce labour costs and necessitate less space and equipment than traditional methods.

Unfortunately the process was found to be strongly formulation dependent, each formulation requiring extensive development work before it could be transferred successfully from traditional to fluidised bed granulation. One major reason for these problems is that fluidised bed granulation is a multistage operation requiring strict control over each process variable to enable a suitable granule to be produced each time. As a consequence, the process is not extensively used. It is felt that investigations into the basic underlying mechanisms would have enabled industry to gain sufficient knowledge to overcome their problems.

Research into the process has mainly been involved with assessing the independent effect of each variable on granule quality; although it has been commented that the effect of many of the variables may be interrelated (Scott et al, 1964; Ormós, Pataki and Csukás, 1973a). It is important to clarify what these effects are since in the literature evidence is conflicting as can be seen in the published literature reviewed in section 1.4.3. Many of these anomalies may be due to differences in the various design and size of granulator used. In order to resolve these anomalies all the possible variables need to be investigated to assess their combined effects in this present system. However, since there are so many possibilities only those properties which, in the light of previous work, were considered to have a marked effect were selected. After considering

the literature it was concluded that seven variables were likely to have the most significant effect upon granule quality. These were chosen for further examination in this work and are listed below.

1. Granulating solution concentration
2. Nozzle size
3. Atomising air pressure
4. Granulating solution temperature
5. Height of nozzle above air distribution grid
6. Fluidising air flow rate
7. Fluidising air temperature

A convenient method for assessing the above factors is the use of an experiment of Factorial Design, since a maximum amount of information, including factor interactions, can be gained from the least number of experiments. A factorial design of 2^n is the most useful initially since it acts as a screening experiment. Before this can be achieved a series of commissioning and preliminary value-searching experiments are required to enable two values (one high and one low) for each variable under investigation to be obtained. This was carried out and the complete 2^7 factorial designed experiment (128 runs) was performed. The resulting granules were assessed as described in section 2.4; these tests were chosen to give an insight into those granule flow properties relevant to tableting. After analysis of the results three categories of granules could be identified, broadly classified as "good", " intermediate", "poor". Batches of granules representative of these categories were compressed and the tablets assessed.

3.1.1. Factorial Design Theory

In a factorial experiment the effects of different factors are investigated simultaneously instead of varying one factor at a time whilst keeping the others constant. The actual method consists of carrying out all the possible combinations that can be formed from the different factors. It is perhaps useful at this point to define several terms which will be used. A factor is an actual process variable and is tested at various levels or values. The specific combination of factor levels is termed a treatment combination. The

advantages of a factorial experiment, in general, are:-.

1. More efficient than a one factor at a time experiment.
2. All data is combined to estimate the effects of the individual factors.
3. Information is obtained on possible interactions between factors.

These advantages become even more pronounced as the number of levels of each factor is increased. A factorial experiment is thus one in which all levels of a given factor are combined with all levels of every other factor in the experiment.

A special type of complete factorial design is one in which 'n' factors are each investigated at just two levels, these two levels being chosen at points near their upper and lower extremes and not at random. There are then 2^n treatment combinations. For example if three factors were investigated it would entail 8 experiments (2 x 2 x 2) with each experiment having its specific factor combination. There is a standard notation used for designation of the treatment combination. An appropriate small letter represents a factor at a high level whilst absence of such a letter corresponds to that factor at its lower level. Thus, if three factors A, B, C were being investigated a combination of ab represents 'A' and 'B' at a high level and 'C' at a low level. The symbol (I) is normally used when all factors are at the low level. A different notation and terminology is used in this thesis.

As previously stated in Section 3.1, the overall objective of an experiment of 2^n factorial design is to obtain a general picture of those factors which exert a significant effect upon a process. It is particularly useful when a large number of factors (as in FBG) have to be considered, since it would require too many tests to fully assess each factor. Therefore in many projects it enables a more thorough understanding of a particular process to be gained thus forming a sound basis for future work.

Generally it is advisable to replicate each individual experiment although when many factors are being assessed this may not be practical. In the latter case an estimation of the error can be calculated in the final analysis. Replication in this case was not performed due to the large number of experiments required in this 2^7 design. The results obtained are, however, still meaningful without duplication.

3.2. INITIAL FLUIDISED BED GRANULATOR COMMISSIONING EXPERIMENTS

A series of commissioning experiments were performed in order to gain practical knowledge and sufficient data from the equipment for the future work envisaged. The following section describes those experiments, the results obtained and their inference for future work.

3.2.1 Formulation

A simple formulation of lactose and maize starch was chosen since each is widely accepted and used in the pharmaceutical industry, also these materials are frequently incorporated together in placebo tablets.

Test formulae were conventionally wet granulated in a planetary mixer (Kenwood Model AE 125, 1/4 H.P.) using 250 ml of either a 5% w/v aqueous PVP or 5% w/v aqueous starch mucilage solution (Snowflake, C.P.C.*, Manchester). The granules produced had excellent flow and compression properties confirming the selection of the formula:-

Lactose	800 g
Maize Starch	200 g
PVP or Starch	12.5 g

PVP was selected as the binder for use in the fluidised bed granulator since it has been shown to have better adhesive qualities (Davies and Gloor, 1972) and, from a practical viewpoint, is much easier to prepare in large quantities than "Snowflake" starch mucilage. This formulation was successfully transferred to the fluidised bed granulator.

It was now necessary to evaluate the working of this formulation in the FBG. This preliminary work was performed in two sections.

3.2.2 Preliminary Granule Preparation

Some process values were fixed by the design of the apparatus, others were initially selected from a knowledge of the operating conditions of the process within the pharmaceutical industry. A precis of the experiments performed in this section is shown in Table 3.1. This preliminary investigation provided the necessary information required since with only slight modifications to the

*Corn Products Corporation

Table 3.1. Preliminary Granule Preparation Investigation

Expt. No.	Atomising Air Pressure (bar)	Fluidising Air Temperature (°C)	Nozzle Combination *	Siphon Height (mm)	Fluidising Air Flow Rate ($m^3 s^{-1}$)	Quantity of 5% $^{w}/_{v}$ PVP Solution (ml)	Charge Size (g)	Height Above Distribution Grid (mm)	Inference
1	1.33	45	1A	150	18.8×10^{-3}	250	1000	450	Granule formed containing large quantity fines. Addition rate of granulating solution slow
2	1.67	60	1A	150	18.8×10^{-3}	250	1000	450	Nozzle blocked. Larger nozzle size required
3	1.67	60	1	150	18.8×10^{-3}	250	1000	450	Granule formed
4	1.67	45	1	100	18.8×10^{-3}	250	1000	450	Acceptable quality granule produced

* See Table 2.1

initial values of atomising air pressure, nozzle size and siphon height a granule of acceptable quality was finally produced.

3.2.3 Investigation into Formulation Charge Size.

Based on the results from experiments in section 3.2.2, an investigation into batch size was performed, the details of which are shown in Table 3.2. The proportion of granulating solution to batch size was kept constant for each size investigated. The granule size distributions are displayed by histogram in Fig. 3.1.

The purpose of this experiment was to select an optimum powder charge size for granulation which would allow a certain degree of flexibility of fluidisation $\swarrow^{\text{air flow rate}}$ without producing any significant entrainment of powder into the filter sock at high velocities or inability to suspend a wetted powder mass at lower values. The 250g and 500g charge sizes were eliminated since the small bulk of powder allowed the spray solution to wet the sides of the container. This enabled powder to build up in layers on the side of the product container without actually becoming fluidised. The outcome of this was the production of excessively large agglomerates due to overwetting ; this is reflected in the size distribution data in Fig. 3.1. The final granulation was therefore of unsuitable quality for tableting purposes. A further disadvantage of these charge sizes was that a small increase in fluidisation $\swarrow^{\text{air flow rate}}$ produced a significant degree of entrainment of powder to the filter sock. Although the size distribution of the 1250g charge was of acceptable quality the fluidisation air flow rates required for this, and the 1500g charge, were rather high. These high flow rates were close to the maximum output attainable by the granulator fan. It was thought therefore that there would not be sufficient flexibility in air flow rates for subsequent experiments.

The 750g charge was selected since this gave a granulation of excellent size distribution as shown in Fig. 3.1, whereas the 1000g charge contained a high proportion of oversize granules. Additionally, the 750g charge required a suitable air flow rate and was of sufficient weight to enable large numbers of samples to be removed for the necessary granule assessment tests.

Table 3.2. Charge Size Experimentation Details

Expt. No.	Charge Size (g)	Atomising Air Pressure (bar)	Fluidising Air Temperature (°C)	Nozzle Combination *	Siphon Height (mm)	Fluidising Air Flow Rate ($m^3 s^{-1}$)	Quantity of 5% $^{w}/_{v}$ PVP Solution Added (ml)	Height Above Distribution Grid (mm)
1	250	1.67	45	1	100	16.6×10^{-3}	62.5	450
2	500	1.67	45	1	100	17.7×10^{-3}	125.0	450
3	750	1.67	45	1	100	18.8×10^{-3}	187.5	450
4	1000	1.67	45	1	100	19.8×10^{-3}	250.0	450
5	1250	1.67	45	1	100	22.5×10^{-3}	312.5	450
6	1500	1.67	45	1	100	26.5×10^{-3}	375.0	450

*See Table 2.1.

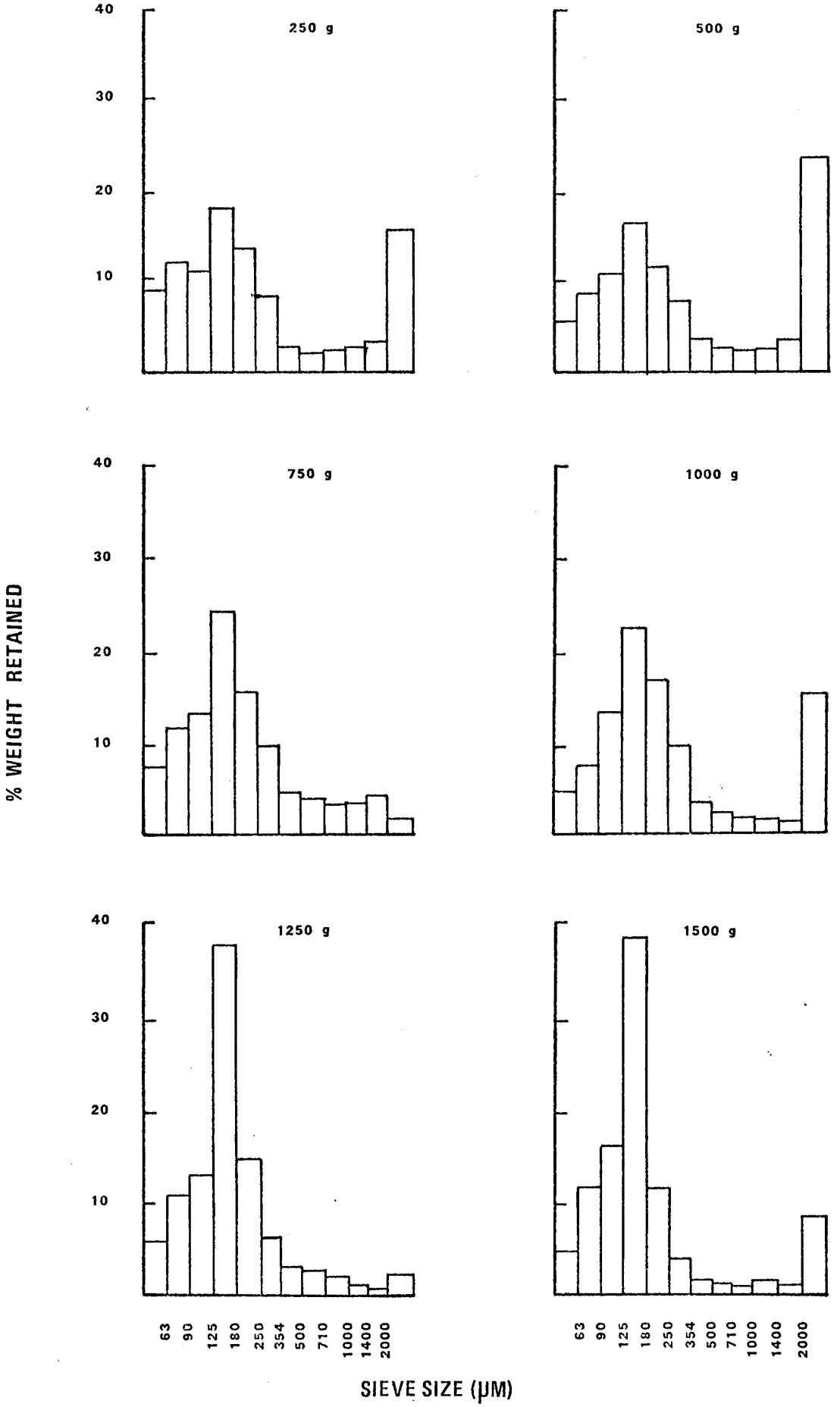


Fig. 3.1 Display of the effect of batch size on granule size distribution

3.2.4 Preliminary Screening of Process Variables

The aim of this section was to obtain two widely differing values for each of the seven variables selected for the 2^7 factorial designed experiment. To achieve this, a series of value searching experiments were performed to assess how far it was possible to alter the value of each variable whilst still producing a granule. This is essential since, if from an extreme combination, gross overwetting occurs, it would be impossible to obtain any quantitative data from the granule tests. The knowledge gained during the granulations performed in section 3.2.2 was of considerable help in the early stages of the variable screening. A summary of the results of these screening experiments and their inference are summarised in Table 3.3.

3.3 EXPERIMENT OF 2^7 FACTORIAL DESIGN

3.3.1 Procedure for Granulation

The properties not selected for further investigation were chosen and held unchanged throughout the 2^7 factorial designed experiment. Their values are shown in Table 3.4.

Table 3.4. Optimised values of the parameters remaining unchanged during the factorial designed experiment

PARAMETER	VALUE
Weight of Powder Charge	750 g
Siphon Height	100 mm
Quantity of granulating solution (5% $^{w}/_{v}$ solution)	170 ml
(10% $^{w}/_{v}$ solution)	85 ml
Spray Nozzle Valve aperture	fully open
DRYING CONDITIONS	
(a) Drying air flow rate	$30 \times 10^{-3} m^3 s^{-1}$
(b) Drying air temperature	65°C
(c) Granule dried to a bowl temperature of	45°C

Table 3.3. Summary of the screening experiments and their influence upon selection of variable values

No.	VARIABLE	RESULTS AND THEIR INFERENCE	
		LOW LEVEL VALUE	HIGH LEVEL VALUE
1.	Concentration Granulating Solution	A maximum of only 170 ml of liquid could be added to the system under any variable conditions without producing an overwetted mass. A commonly used concentration of 5% $^{w}/_{v}$ PVP was selected.	Concentrations in excess of 10% $^{w}/_{v}$ gave flow and atomisation problems resulting in nozzle blockage.
2.	Nozzle Combination *	The '1A' combination tended to block therefore used the '1' system.	The '2' combination was selected since the next largest nozzle ('4') in the series produced too great a flow rate thereby overwetting the mix.
3.	Atomising Air Pressure	Values less than 1.67 bar gave a greater chance of nozzle blockage.	Values greater than 2.67 bar increased the spray cone width such that it sprayed the product container walls. Addition rates of granulating solution were also markedly increased leading to gross overwetting.
4.	Granulating Solution Temperature	A value of 30°C was selected.	A maximum value of 60°C was used.
		The values selected for the low and high levels were within the maximum range commonly used within the pharmaceutical industry.	
5.	Height of Spray Nozzle Above Distribution Grid	Heights less than 300 mm produced clogging of the distribution grid.	A maximum height of 450 mm was available due to the product container dimensions.
6.	Fluidising Air flow Rate	Values less than $18 \times 10^{-3} m^3 s^{-1}$ were inadequate to fluidise a wetted mass.	Values higher than $25 \times 10^{-3} m^3 s^{-1}$ gave excessive powder entrainment on the filter sock lining which could not be rectified by shakedown
7.	Fluidising Air Temperature	Lower temperatures (<30°C) enhance the chance of overwetting especially when a large nozzle combination is used.	Temperatures in excess of 60°C produce nozzle blockage and are also incomparable with values used in industry.

* See Table 2.1

The seven factors chosen for further investigation are listed in Table 3.5 along with two distinctly different values previously obtained from preliminary studies (section 3.2.4). The interrelationship between these factors was investigated using the 2^7 factorial designed experiment in a randomised manner to eliminate any bias.

Table 3.5 The values of the factors used in the experimental runs.

	Number						
	1	2	3	4	5	6	7
Key	Concn. Granulating Soln. (% w/v)	Nozzle Set-up Combination (*)	Atomising Air Pressure (bar)	Temp. Granulating Soln. (°C)	Nozzle Height Above Distribution Plate (mm)	Fluidising Air Flow Rate ($m^3 s^{-1}$)	Fluidising Air Temp. (°C)
Low Value -	5	1	1.67	30	300	18×10^{-3}	30
High Value +	10	2	2.67	60	450	25×10^{-3}	60

* Refer to Table 2.1

The basic procedure for each run was as follows. The starch/lactose charge was presifted through a 1.0 mm sieve and added to the product container after the inlet air temperature had stabilised at the run value. Prior to the addition of granulating solution the powders in the container were mixed by fluidisation for 30 seconds. The granulating solution was then sprayed into the bed at the preset run temperature, concentration and atomising air pressure, using a constant siphon height of 100 mm. The required quantity of granulating solution was drawn in and its addition rate measured. At the end of the spraying phase the supply of atomising air was stopped and both the fluidising air temperature and flow rate increased to 65°C and 30×10^{-3} $m^3 s^{-1}$ respectively. Each granulation was so dried until a bowl temperature of 45°C was reached, equivalent to a final moisture content of between 2.0 and 2.5 %, as determined by loss on drying. using a Vacuum Moisture Tester, E164 (Townson and Mercer Ltd, Croydon) at 105°C for 15 minutes.

3.3.2. Granule Testing

A set of granule tests were performed to characterise the granulations produced from each combination. These granule tests were those outlined in section 2.4.

3.4. RESULTS

3.4.1. Data

The data obtained from the tests (section 3.3.2) carried out on each batch of granules are listed in Appendix III with a précis of the range of values shown in Table 3.6.

Table 3.6 Range of granule properties

Property	Measured value	
	Minimum	Maximum
A. Mean particle size	107 μm	210 μm
B. Poured Bulk Density (ρp)	0.45 g ml^{-1}	0.59 g ml^{-1}
C. Tap Bulk Density (ρt)	0.55 g ml^{-1}	0.78 g ml^{-1}
D. Hausner Ratio ($\rho t/\rho p$)	1.17	1.39
E. Angle of repose	45°	62°
F. Rate of flow through 12 mm circular orifice	5.1 g s^{-1}	16.3 g s^{-1}

As can be seen in Appendix III a large amount of data was generated. From these data it was essential to extract information which could be used as a general guide to overall granule quality. For this work the definition of granule quality was taken to be the ability or inability to produce satisfactory die filling since this is the major factor which affects tablet weight variation and is second only in importance to compression properties. Since no one granule test can adequately reflect this property a combination of several tests must be used. In order to aid this selection, scattergrams were constructed to show visually the interrelationships between each set of data. The statistics used to summarise the relationship in such a system are the regression equation and the correlation coefficient (r). The regression equation is a mathematical formula for predicting the most likely value of one variable from the value of the other variable for a given case. The correlation coefficient measures the

degree to which the regression equation produces accurate predictions. As such it is also interpreted as a measure of the strength of association between the two variables. The information generated from this simple statistical procedure thus enabled:-

(a) The selection of those sets of data to be used in the analysis of the experiment of 2^7 design.

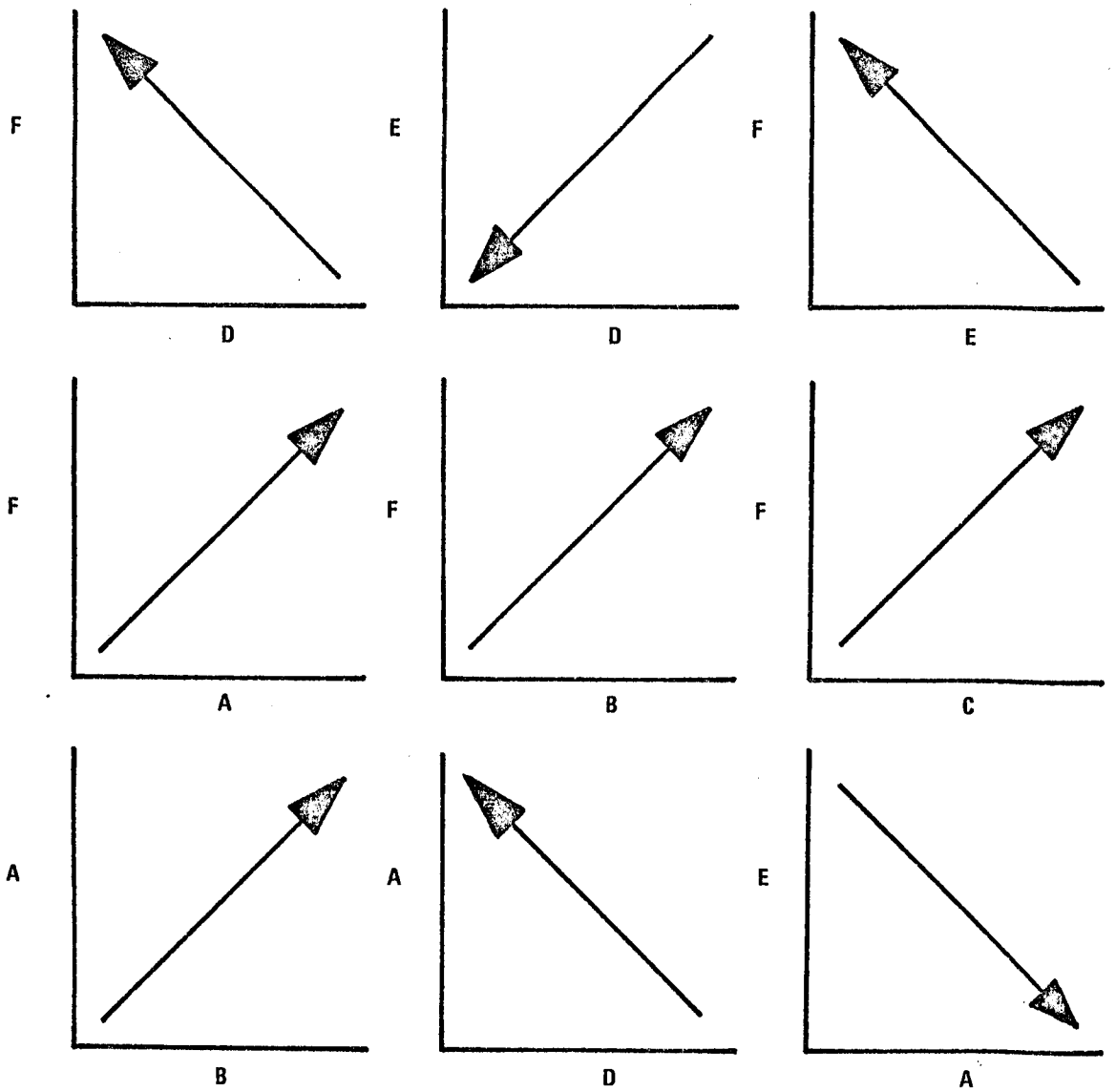
(b) The identification of those values obtained from the granule tests indicative of a good quality granule.

(c) A quick visual method of showing the above.

For several granule batches no experimental values could be determined. All such combinations where this occurred were omitted from further analysis. The remaining data were inputed into a computer program which plotted scattergrams and then calculated the correlation coefficient, together with the values of slope and intercept for the regression equation.

The absolute values of poured and tap density were not selected for further use in the later analysis of the 2^7 experiment. In practice neither value is indicative of a granule's ability to give a uniform die fill since during the initial filling process the actual granule density lies between, or is lower than, these two values. Their elimination helped reduce the amount of data without affecting the overall assessment of granule quality. Flow through the minimum possible orifice did not yield any useful information and therefore was also eliminated from any further analysis.

Those sets of data showing a significant degree of association (at the 0.001 level) are listed in Table 3.7. A graphical representation of each of these significant associations is given in Fig. 3.2 together with an indication of the desired granule properties. The correlations indicate the close interrelationship between mean particle size, angle of repose, flow, density values and Hausner Ratio. These significant correlations are as expected since as stated in section 2.4, particle size distribution influences overall flow and density values. Although particle size distribution might therefore be considered as solely an indication of granule quality it is felt that combined with the values of flow through an orifice, angle of repose and Hausner Ratio, a complete characterisation of each granulation is obtained.



Key A - Mean Particle Size
B - Poured Bulk Density
C - Tap Down Density
D - Hausner Ratio
E - Angle of Repose
F - Flow through Orifice

Fig. 3.2 Graphical interpretation of significant associations stated in Table 3.7. The arrow indicates the desired granule quality.

Table 3.7 Table showing those sets of data with a significant degree of association at the 0.001 level

(For $\phi = 100$, $r = 0.321$, $P < 0.001$)

Correlation Coefficient (r)			
>0.8	>0.6 - 0.8	>0.4 - 0.6	>0.321
D v E	A v F	A v B	A v E
D v F	B v F	A v D	
	E v F	C v F	

Key
- A. Mean Particle Size
- B. Poured Bulk density
- C. Tap down density
- D. Hausner Ratio
- E. Angle of Repose
- F. Flow through orifice

One possible criticism which could be levelled at the above statistical procedure is that several pieces of information were omitted in the calculation of the coefficient r since for some granulations a number of values could not be measured (i.e. the powder would not flow). A further statistical technique was therefore applied to validate the results in Table 3.7. The test used was Pearsons product moment correlation. This involves arranging the data into rank order such that each of the 128 batches had a numerical value. Those granule batches which were assessed as having the best pharmaceutical properties were numbered 1, the other poorer granules were numbered from 2 to 128 respectively with number 128 being the poorest.

The results of Pearsons analysis are shown in Table 3.8. A comparison of these with the results in Table 3.7 confirm that the omission of those runs where no test data could be measured had no significant effect.

Table 3.8 Table of those sets of data having significant (0.001 level) Pearsons product moment correlations

(For ϕ = 100, r = 0.321, P < 0.001)

Pearsons Moment correlation coefficient			
>0.8	> 0.6 - 0.8	> 0.4 - 0.6	>0.321
D v F		A v B	A v C
E v F	D v E	A v F	A v D
			A v E
			B v F

Illustrative rank order technique for initial interpretation of data.

An illustrative technique was employed to obtain an overall value of granule quality for each granule batch. This involved using the rank order values previously generated during Pearsons Analysis (see page 94) for four granule tests. The granule tests were selected from regression analysis results (Table 3.7), scattergram diagrams (Fig. 3.2) and the criteria for defining a good granule within the range of values observed as defined on Page 91. These tests are:-

* a larger mean particle size
* a smaller angle of repose
* a faster flow through orifice
* a lower Hausner ratio (i.e. less friction)

The rank order of these tests for each granulation were averaged and a chart tabulated with the best overall granule performance at the top and the worst at the bottom (Table 3.9). For clarity only the first and last twenty runs have been reproduced since no trends were observed from the intermediate results. Also shown on the chart is a summary of the process variable levels used in each granule batch manufacture. A filled square (■) represents a high level shown as + in Table 3.5 and an open square (□) a low value as defined in Table

Table 3.9 Granulation properties listed in overall rank order

Overall rank order	Run number	Mean particle size	Angle of repose	Orifice flow rate	Hausner ratio	Overall rank mean	Process variable format						
							1	2	3	4	5	6	7
1	40	3	4	2	1	2.5							
2	36	1	1	1	8.5	2.9							
3	98	2	5	13	7	6.8							
4	102	7	7	17	6	9.3							
5	101	6	25	4	5	10							
6	26	4	13.5	3	20	10.1							
7	90	10	15	14	3.5	10.6							
8	97	12.5	2	23	13	12.6							
9	34	12.5	17.5	19	2	12.8							
10	104	20.5	16	8	13	14.4							
11	89	26.5	3	26	10	16.4							
12	30	20.5	19	11	15.5	16.5							
13	32	14	9	9	36	17							
14	37	44.5	11	5	8.5	17.3							
15	93	26.5	17.5	25	3.5	18.1							
16	39	44.5	12	6	11	18.4							
17	100	10	34.5	15	30.5	22.5							
18	35	16	32	16	26.5	22.6							
19	31	51.5	6	10	23.5	22.8							
20	92	26.5	40.5	12	19	24.5							
109	76	71.5	111	117.5	109.5	99.9							
110	15	61.5	117	117.5	104	100							
111	58	57.5	112	117.5	116	100.8							
112	4	61.5	111	117.5	114.5	101.1							
113	49	81	97	117.5	113	102.1							
114	72	61.5	110	117.5	120	102.3							
115	120	66	123.5	106	117	103.1							
116	78	101	104	104	105	103.5							
117	6	66	114	117.5	124.5	105.5							
118	64	54	123.5	117.5	127.5	105.6							
119	12	87.5	115	94	127.5	106							
120	9	69	118	117.5	121.5	106.5							
121	10	75.5	123.5	117.5	123	109.9							
122	56	98	116	117.5	124.5	114							
123	74	108.5	123.5	117.5	107	114.1							
124	80	119	123.5	117.5	106	116.5							
125	53	105	123.5	117.5	121.5	116.9							
126	52	127	123.5	117.5	114.5	120.6							
127	50	128	123.5	117.5	119	122							
128	54	124	123.5	117.5	126	122.8							

3.5. By arranging the information in this way several trends were observed and tentative conclusions deduced relating overall granule quality with manufacturing conditions. By scanning down the list certain properties appear in greater abundance at one end or other of the chart. These obvious concentrations of either symbol indicate which conditions are likely to produce a good granule and those to produce a poor one.

(i) Conditions producing good quality granules

These are shown at the top of the chart in Table 3.9 for example the run of white squares in column 1 and filled in squares in column 2; in fact the best 37 granulations were all produced by a dilute 5% granulating solution and the best 27 by the larger spray set-up. The three variables found to have a profound effect in producing a good granule are listed in Table 3.10.

Table 3.10 Variables found likely to produce a good quality granule

Process Variable Code (Table 3.5)	Variable	Value Level (see Table 3.5)	Figure Symbol (Table 3.9)
1	Granulating solution concentration	Low	□
2	Nozzle size	High	■
6	Fluidising air flow rate	Low	□

(ii) Conditions producing poor quality granules

Five variables were found to influence the production of poor granules. These are listed in Table 3.11.

Table 3.11 Variables found likely to produce a poor quality granule

Process Variable Code	Variable	Value Level (see Table 3.5)	Figure Symbol (Table 3.9)
1	Granulating solution concentration	High	■
2	Nozzle size	Low	□
3	Atomising air pressure	Low	□
6	Fluidising air flow rate	High	■
7	Fluidising air temperature	High	■

These observations and results are discussed in section 3.7.

3.4.2 Yates' Analysis

The above conclusions are only of a qualitative nature and in order to statistically analyse the experimental data a systematic method of estimating the effects and of performing the analysis of variance must be applied. This is achieved by using Yates' Method (1937).

Procedure for Yates' Method of Analysis

The procedure and an account of the theoretical considerations of the method can be found in many textbooks (e.g. Chatfield 1970, Hicks 1964, Cochran and Cox 1966). The treatment combinations are firstly listed in the systematic manner of Yates (1937). Since seven factors (variables) were investigated 7 columns must be generated from the preceding column by repeating the following technique. The first 2^6 (=64) numbers in each subsequent column are the sums of the successive pairs of numbers in the preceeding column. The next 64 numbers are the differences between the successive pairs, the first number being subtracted from the second. The final column (number 7) gives the effect totals corresponding to the particular treatment combination. Each effect can then be estimated by dividing the effect totals by 2^6. The sum of the squares of each effect is then obtained by squaring the effect total and dividing by 2^7 (128). A computer programme was developed for calculating these columns since the above procedure had to be repeated for each of the four sets of granule test data used to reflect the quality of a granulation. A typical print out for such a set of granule test data is shown in Appendix IV.

Unfortunately this factorial design was so large that it would have been extremely difficult to replicate the experiments therefore a residual variation must be estimated since the main effects account for all the degrees of freedom. To overcome this it is generally accepted that interactions involving two factors are rarely of practical significance thus enabling a residual mean square to be calculated. For this analysis the sum of squares of the effects for the 1, 2, and 3 factors together with all other effects greater than a preset value were omitted. The preset value was selected after reviewing the sum of squares of the effects since several of these were large and therefore could not be used for calculating the residual mean square as they themselves may be significant. A series of 'F' ratios can

then be obtained by dividing the remaining effects mean squares by the calculated residual mean square thus enabling those effects which are significantly large to be determined.

The above procedure was performed on each of the four sets of granule test data. A summary of the 1 and 2 factor 'F' ratio values for each granule test is shown in Table 3.12. The multifactor effects, although found to exert some effect were excluded from this table since their interpretation is complex and therefore of little practical importance.

The results of Yates' Analysis therefore shows that of the seven factors investigated five had a highly significant effect on granule quality. These factors are:

1. concentration of granulating solution
2. nozzle set-up combination
3. atomising air pressure
6. fluidising air flow rate
7. fluidising air temperature

The other two factors, temperature of granulating solution and nozzle height above distribution grid, did not exert such a significant effect upon granule quality. A review of the two factor interactions show that only those containing certain combinations of two of the above five factors have a significant effect. These conclusions are discussed in section 3.7.

It is important, however, to emphasise that although the value of the 'F'-ratios will quantify the degree of influence that any particular process variable has on granule quality, it does not indicate the "direction" of that association. For example a high 'F' ratio shows that the type of nozzle has a very significant effect but it does not show whether a good granule is produced by the large or small nozzle. This information can be found, however, from the qualitative information in Table 3.9.

3.5 TORQUE MEASUREMENT AS A METHOD OF ASSESSING GRANULE QUALITY

3.5.1 Torque Measurement

The application of torque measurements in the assessment of granule properties is written as a separate section since it is not yet an established technique.

The torque arm mixer and the procedure for taking a torque reading are described in section 2.4.5. For each of the 128 granule

Table 3.12 Summary of the 'F' ratio values for 1 and 2 Factor Effects.

Process Effect Variable Code (see Table 3.5)	Flow	Angle of Repose	Mean Particle size	Hausner Ratio	Mean Ratio	Significance Level
1	190.0	14.7	246.4	131.8	145.7	******
2	405.0	13.3	63.1	254.2	183.9	******
3	28.0	3.7	14.3	70.9	29.2	******
4	1.9	0	9.8	4.7	4.1	*
5	1.9	5.8	17.1	1.6	6.6	**
6	42.0	18.0	30.9	41.6	33.1	******
7	50.7	16.1	9.6	62.5	34.7	******
1+2	3.8	24.9	29.6	0.6	14.7	******
1+3	7.5	0.8	2.9	1.9	3.3	
1+4	0	1.8	0.6	2.3	1.2	
1+5	0.7	2.2	2.2	0.1	1.3	
1+6	0.0	15.4	7.9	0.2	5.9	**
1+7	3.8	17.3	21.6	0.5	10.8	*****
2+3	54.9	3.5	0.3	28.8	21.9	******
2+4	5.3	0	0.1	4.4	2.4	
2+5	2.5	5.6	3.0	2.8	3.5	
2+6	52.3	17.9	16.7	89.9	44.2	******
2+7	13.2	24.1	0.9	20.6	14.7	******
3+4	0.2	2.3	1.7	6.4	2.6	
3+5	11.3	4.0	0.5	7.4	5.8	**
3+6	1.7	1.2	0.2	0	0.8	
3+7	1.1	1.2	0.1	0	0.6	
4+5	0.7	1.2	0.0	3.3	1.3	
4+6	0.1	2.0	1.4	0.1	0.9	
4+7	0.4	1.9	0.7	0.8	0.9	
5+6	0.3	1.7	0	0.3	0.6	
5+7	2.3	1.8	3.9	2.7	2.7	
6+7	0.9	13.9	7.4	1.2	5.8	**

F 0.001, 1, 60 = 11.97 ******

F 0.0025, 1, 60 = 9.96 *****

F 0.005, 1, 60 = 8.50 ****

F 0.01, 1, 60 = 7.08 ***

F 0.025, 1, 60 = 5.29 **

F 0.05, 1, 60 = 4.00 *

batches a torque reading was measured with a) the mixer arm rotating at 120 revs/min, b) the bowl rotating at 30 revs/min and c) the bowl and mixer arm counter-rotating at these speeds.

Two series of torque values were taken for each granulation: (i) the granulation as produced and (ii) with all large granules exceeding 2000 μm removed.

3.5.2 Results

The six torque values measured for each of the 128 granule batches are listed in Appendix V. The degree of association between each of the torque readings and the previously generated granule test data (Appendix III) was assessed by regression analysis as described in section 3.4. A torque value could not be recorded for some batches due to the constant variations in readings during measurement and these were omitted from the analysis.

Those sets of data showing a significant degree of association (at the 99.9% level) are listed in Table 3.13.

Table 3.13

Table of torque and conventional granule test data showing a significant degree of association at the 0.001 level.

(For $\emptyset = 100$, $r = 0.321$, $P < 0.001$)

CORRELATION COEFFICIENT (r)					
> 0.8	>0.7	>0.6	>0.5	>0.4	>0.321
B v G	B v L	D v H	B v H	A v H	A v G
B v I	C v G	F v K	B v K	A v K	A v J
B v J	C v J		D v K	E v K	
C v I	C v L		E v H		
	F v G				
	F v H				
	F v I				
	F v J				
	F v L				

Key	Normal Granule Test	Torque
	A. Mean Particle Size	G. Sieved Bowl Torque
	B. Poured Bulk Density	H. Sieved Paddle Torque
	C. Tap Down Density	I. Sieved Bowl/Paddle Torque
	D. Hausner Ratio	J. Non Sieved Bowl Torque
	E. Angle of Repose	K. Non Sieved Paddle Torque
	F Flow through orifice	L. Non Sieved Bowl/Paddle Torque.

It is apparent from this table that there is a strong correlation between a large number of granule tests and torque readings. As previously stated (section 2.4.5.) powder viscosity devices have been used in granulation assessment for the testing of widely different materials. These results highlight the possible use of torque measurement as a method of characterising granular materials having physical properties within a limited range. The torque readings measured when only the paddle was revolving had significant associations, at the 99.9% level, with five sets of granule test data, whilst the torques generated with the bowl and bowl/paddle had only four and three significant correlations respectively. The 5 correlations are with:-

A) Mean particle size

B) Poured Bulk density

D) Hausner Ratio

E) Angle of repose

F) Flow through an orifice

A graphical interpretation of these correlations together with an indication of the desired granule properties is shown in Fig. 3.3. This torque value has a further advantage since it is easy to measure and requires only a simple piece of apparatus.

Hence the paddle torque reading can be considered as being a measure of overall granule quality.

Yates' analysis as described in 3.4.2 was then applied to the paddle torque data. The calculated 'F' ratios with corresponding significance are listed in Table 3.14. Close examination of the table shows that a large number of variables exerted a significant effect upon paddle torque and therefore granule quality. The order of magnitude of 'F' ratio was similar to those found in Table 3.12. Concentration of granulating solution and nozzle set up had highly significant effects with 'F' ratios in excess of 80. Atomising air pressure and fluidising air temperature also exerted significant effects ('F' ratios >20) together with the variables, temperature of granulating solution and height of nozzle above distribution grid ('F' ratios: 7.3 and 9.1). Surprisingly the effect of fluidising air flow rate was shown not to have a significant influence upon torque. It is possible that the influence of individual factors may negate each other and this may explain the fluidising air flow rate not having a significant influence upon torque.

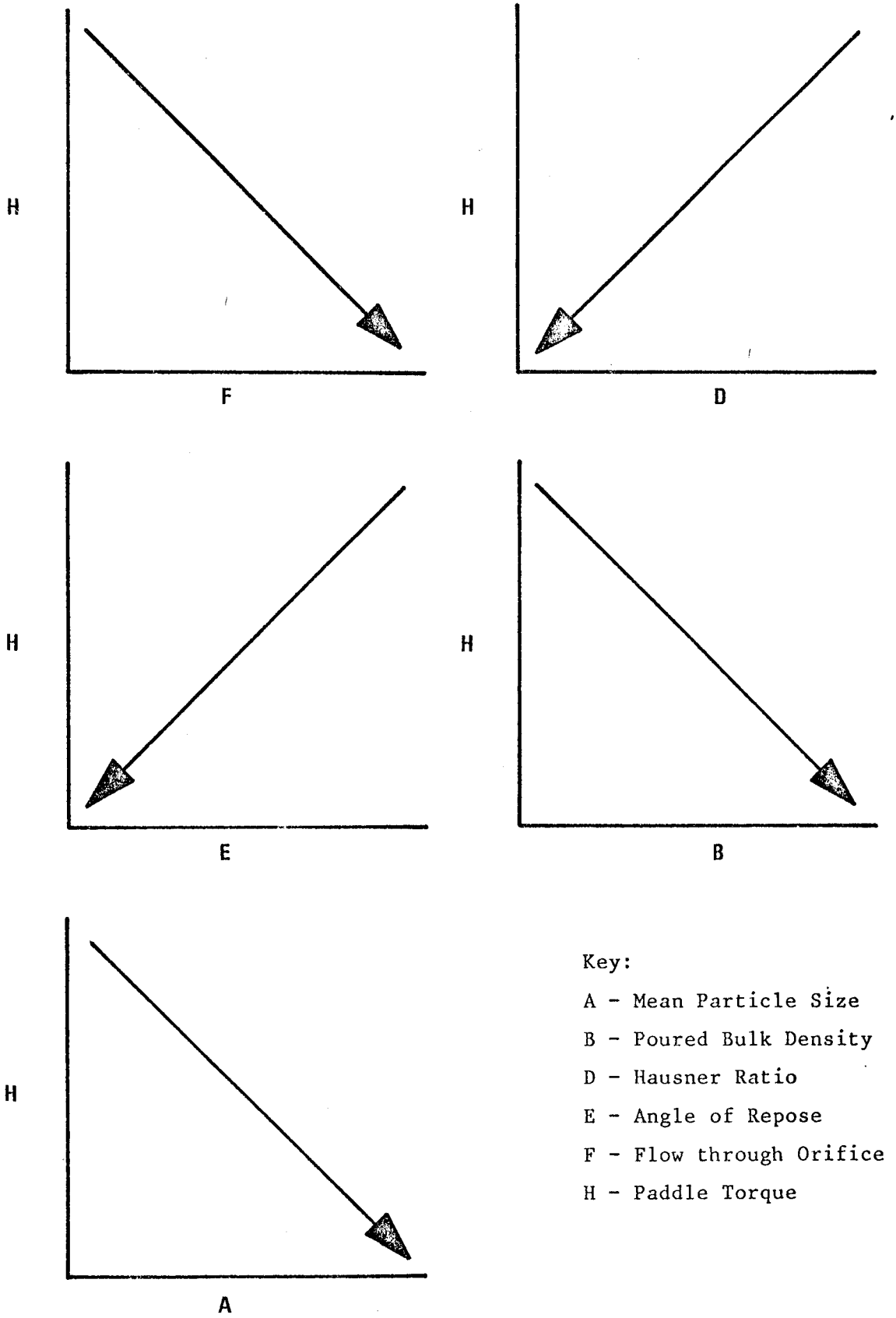


Fig. 3.3. Summary of the five granule tests which showed significant correlation with paddle torque. The arrow head indicates the desired granule quality.

Table 3.14 Summary of the 'F' ratio values for 1 and 2 Factor Effects using the paddle torque data.

PROCESS EFFECT VARIABLE CODE (see Table 3.5)	'F' RATIO	SIGNIFICANCE LEVEL
1	84.6	******
2	97.7	******
3	26.8	******
4	9.1	****
5	7.3	***
6	2.3	
7	20.0	******
1+2	13.1	******
1+3	10.7	*****
1+4	9.8	****
1+5	1.5	
1+6	15.0	******
1+7	3.9	
2+3	5.9	**
2+4	2.7	
2+5	0.6	
2+6	12.5	******
2+7	3.8	
3+4	11.7	*****
3+5	1.9	
3+6	9.9	****
3+7	0.9	
4+5	0.1	
4+6	7.9	***
4+7	2.3	
5+6	0.3	
5+7	2.5	
6+7	0.0	

F 0.001, 1, 60 = 11.97 ******
F 0.0025, 1, 60 = 9.96 *****
F 0.005, 1, 60 = 8.50 ****
F 0.01, 1, 60 = 7.08 ***
F 0.025, 1, 60 = 5.29 **
F 0.05, 1, 60 = 4.00 *

In general the same conclusions were derived from the simple paddle torque data as were previously concluded from Table 3.12 when the results from a number of conventional granule tests were combined for an overall value of granule quality. In order to confirm this supposition the degree of association between the 1 and 2 Factor 'F' ratio effects derived from torque and those derived from conventional granule tests were examined by regression analysis. A significant degree of association between the sets of data was confirmed by a calculated correlation coefficient of 0.96 ($P < 0.001 = 0.58$). To further support this conclusion a paired 't' test was applied to the two sets of data. A calculated 't' value of 1.913 was obtained ($P_{0.05} = 2.06$ for $\emptyset = 27$) thus indicating that there was no significant difference between the two sets of 'F' ratio generated from Yates' analysis by torque measurement or other conventional granule tests.

The conclusion from this experiment has confirmed the great potential of torque measurement as a method of assessing granule quality. It is suggested that further work is necessary to fully evaluate the test by specifically studying particles of various size, shape together with selected sieve fractions. The torque test at present is purely qualitative although it has been shown to be a quick simple technique for measurement of granule quality and therefore could be a beneficial tool in the field of formulation.

It has thus been shown that the torque generated by a paddle revolving in a granule mass can be used as a measure of granule quality.

3.6. TABLETING CHARACTERISTICS

3.6.1. Procedure for Tableting

An assessment of the quality of tableting granules cannot be complete without an investigation of their compression properties. For this reason three distinct batches of granules were chosen to be representative of granule quality as found in section 3.4. The granulations selected were:-

(a) 'good' granules: two granulations (runs 40 and 36) from the top of Table 3.9

(b) 'intermediate granules': runs 23 and 48 from the central region and

(c) 'poor' granules: runs 53 and 54 from the bottom of Table 3.9.

Prior to compression, each batch of granules was passed through

a 2,000 μm screen to remove any large granular material which would otherwise have blocked the hopper. Each granulation was subsequently lubricated by the addition of 0.25 % w/w of magnesium stearate to alleviate punch/die sticking and die friction. Tablets of 11 mm diameter, nominally 450 mg were then prepared at a range of compaction forces up to 310 MPa using an instrumented Manesty BB3B tablet machine (see section 2.6). The punches used were of normal curvature and the machine speed was 20 r.p.m.

3.6.2. Tablet Testing

The physical properties of each set of tablets produced were assessed using the routine tests as described in section 2.7., these tests being:- (a) crushing strength, (b) thickness, (c) weight variation, (d) disintegration time and (e) friability.

3.6.3. Results

(a) Crushing Strength

The crushing strength profiles of the three types of compressed granules are shown in Fig. 3.4. For each granule there is a linear increase up to 2000kg compression force (approx. 205 MPa) after which lamination occurred in some tablets. The poorer granules produced stronger tablets although the difference in strength at normal tableting pressures is small.

(b) Tablet Density

Tablet density was calculated from tablet thickness and weight for each batch of tablets compressed. At any compaction pressure, no significant difference in density (within 1%) could be observed.

(c) Tablet Weight Variation

From the individual weighing of twenty tablets from each compressed batch of granules a coefficient of variation was calculated and plotted against compaction pressure. The poor granulation performed less well over the whole of the compression pressure range particularly values in excess of 1500kg (155 MPa) see Fig. 3.5. This is an indication of poor flow properties thus giving the uneven die fill

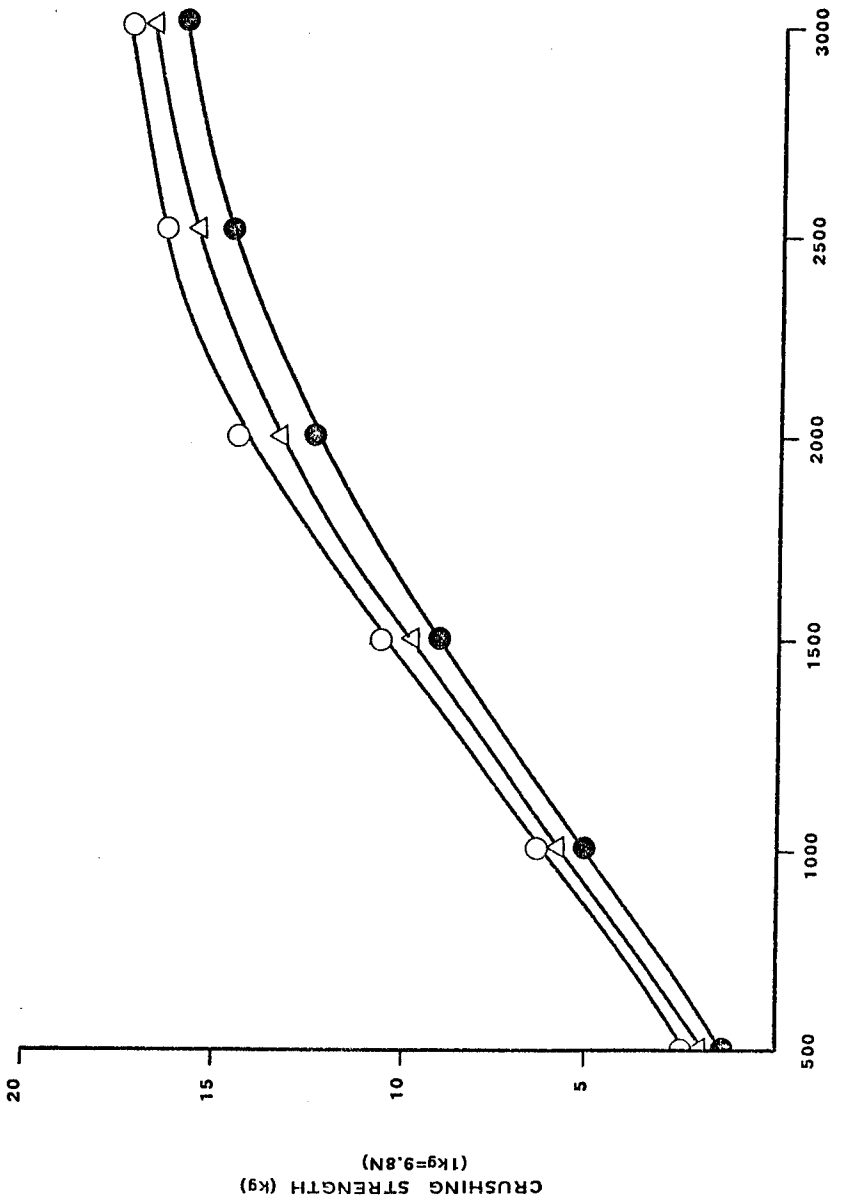


Fig. 3.4. Profile of crushing strength against compression force for good (●), intermediate (△) and poor (○) batches of granules.

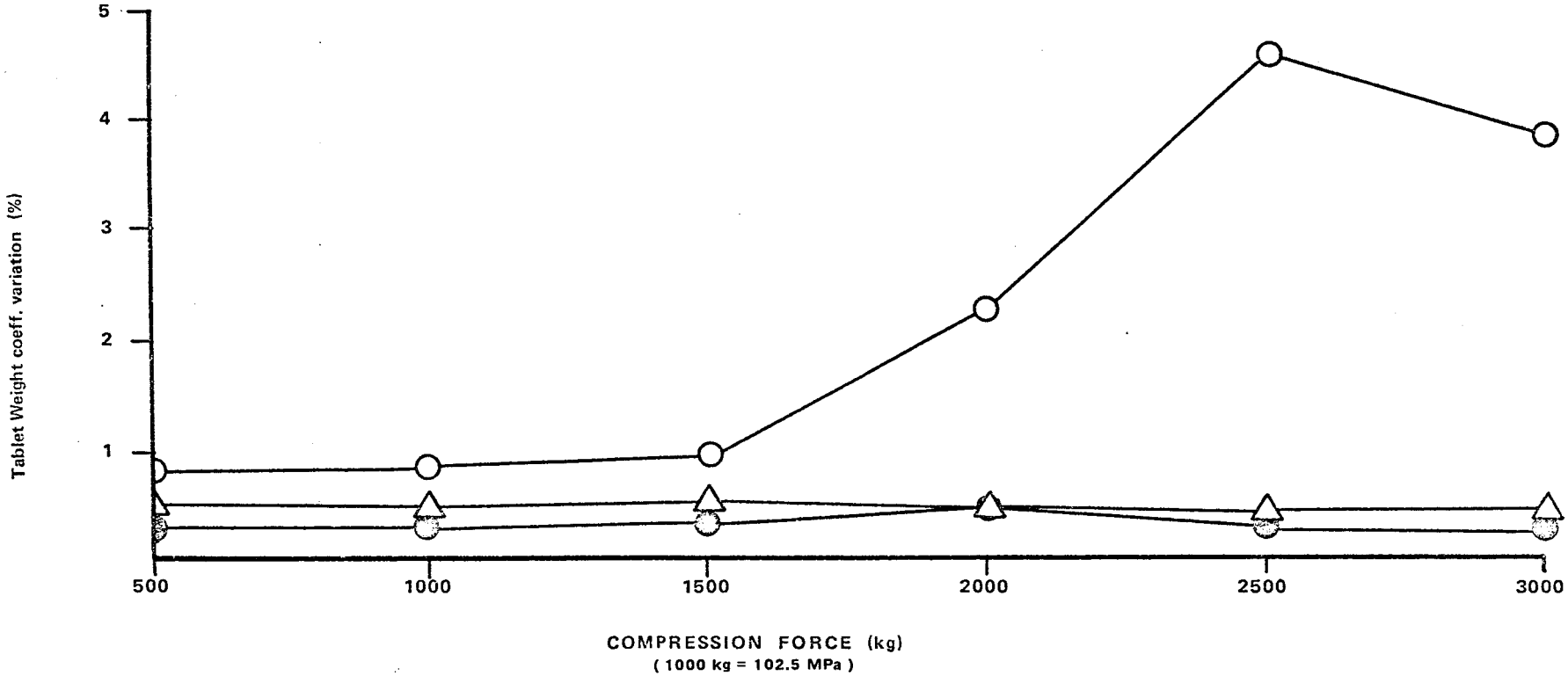


Fig. 3.5. Tablet weight variation for good (●), intermediate (△) and poor (○) granule batches against compression forces.

weight. Thus in high speed compression machines this would become a major problem leading to variation in drug content uniformity.

(d) Disintegration Time

No significant differences could be observed from a plot of disintegration time and compression force. This is probably due to either the formulation used or the inherent variability of the test.

The only general conclusion that could be made is that disintegration time increased with compression force.

(e) Tablet Friability

An examination of changes in percentage loss in weight with compression force showed there to be no significant difference between the granules.

3.6.4 Tableting Conclusions

Significant differences were found between the flow of each category of granule and certain of their tableting characteristics. An examination of the particle size distribution of an example of each category of granule (Fig. 3.6) yields an explanation of these observations. The graph shows that the good granulation had a larger mean particle size and also a large proportion of monosized particles. The poor granulation however still contained a high proportion of the original fine powder. In this latter case this will result in the formation of a larger number of bonds during compaction thus giving slightly high crushing strength values. The tablet weight variation profile shows that the 'poor' granulation performs less well over the whole compaction range. This is an indication of the poorer flow characteristics of the granule.

3.7 DISCUSSION

The process variables which had a significant effect on the quality of granules have been listed, together with their corresponding 'F' ratios, in Table 3.12. From this, two other tables were extracted. Table 3.15 shows all seven single factor variables (Category A) and Table 3.16 shows only the significant two-factor interactions (Category B).

Examination of Table 3.15 shows that the seven single-factor process variables fell into three distinct groups (categorised divisions IA, IIA and IIIA) with regard to the magnitude of their significance upon granule quality.

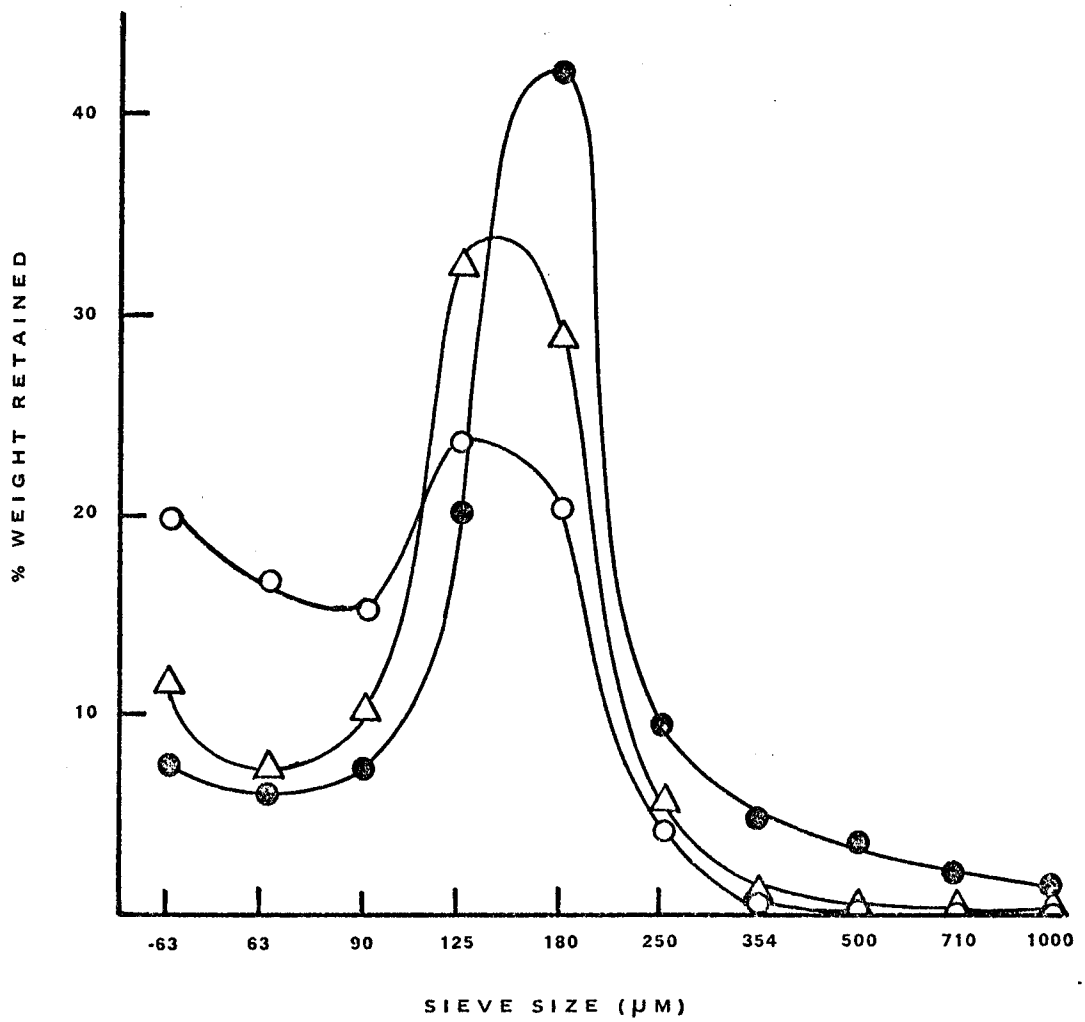


Fig. 3.6. Graph of particle size distribution of examples of good (●), intermediate (△) and poor (○) granule batches.

Table 3.15 One factor process variables arranged in rank order of mean 'F' ratios (from Table 3.12)

DIVISION	FACTOR	VARIABLE	MEAN 'F' RATIO
IA	2	Nozzle combination	183.9
	1	Concentration (volume) granulating solution	145.7
	7	Fluidising air temperature	34.7
IIA	6	Fluidising air flow rate	33.1
	3	Atomising air pressure	29.2
IIIA	4	Temperature granulating solution	6.6
	5	Nozzle height above distribution plate	4.1

The factors in division IA have a very high 'F' ratio value which is indicative of these variables having a profound influence upon granule quality (significance >99.99). Both factors in this division (i.e. nozzle combination and concentration of granulating solution) are interrelated since each influences the amount of liquid added to the system. Consideration of the theoretical mechanism of granulation explains their effect. Table 3.11 shows that a good granule is formed when Factor 2 is at a high level (i.e. the large nozzle combination, thus high rate of liquid addition and larger droplets) and Factor 1 at a low level, i.e. low concentration of granulating solution and therefore a larger total volume of liquid added. The formation of granules depends, in the fluidised bed granulator, upon the successful random collision between particles and droplets with the formation of liquid bridges and, after evaporation, solid bridges. When a low concentration of granulating fluid is sprayed through a larger nozzle combination the number of collisions are greatly increased due to the large volume and increased addition rate of liquid sprayed onto the bed. There is also more liquid available for liquid bridges and this results in a high liquid content at any time. The strength of the final granule will therefore be high and thus disaggregation due to the high friction forces within the bed is less. As the total volume and rate of addition of liquid is increased then a larger number of particles become wetter more quickly and the greater volume of liquid available will produce the Funicular or Capillary state for a longer time.

The three variables in division IIA also have a significant effect upon granule build up. Factor 3 (atomising air pressure) has a similar effect but of lower magnitude to Factors 2 and 1 in division IA since it affects addition rate of granulating liquid due to a siphoning effect. At low air pressures less fluid is added and there is also a reduction in the number of droplets formed since a low pressure will give poorer atomisation of liquid therefore fewer droplets. At the high level the larger atomising pressure enhances the siphon effect and thus the rate of liquid added to the system and the atomisation of the spray are increased thereby improving the probability of successful collision. The other two factors in the second category i.e. 7 (fluidising air temperature) and 6 (fluidising air flow rate) primarily affect the rate of evaporation of liquid from the bed.

Scott et al (1964) derived a general expression for the evaporation rate from an atomised liquid.

$$R_e = \frac{hS\ (Ta - Td)}{\lambda}$$

R_e = Rate of evaporation kg min^{-1} h = overall heat transfer coefficient

S = total surface area of droplet created by atomisation of liquid granulating solution Ta = temperature of inlet air

Td = temperature of surface of the droplet

λ = heat of vaporisation of water

Thus if Ta (i.e. factor 7) is high then the rate of evaporation from the droplets will be high. The smaller droplets will either evaporate before collision or will not wet the particles sufficiently well for a long enough time therefore particle aggregation will be reduced. This was confirmed in this work since with the fluidising air temperature at a high level, i.e. 60°C, there was poorer agglomeration. Associated with this is the amount of liquid incorporated in the liquid bridge since this will be evaporated quickly and bond formation will be affected. At lower temperatures evaporation will be reduced and successful collisions will remain wetter (i.e. at a higher level of water content) for longer thus possibly improving crystal bridge formation due to partial dissolution of the solid. This will therefore increase final solid bridge strength. The multiparticle agglomerate will also be adhesive for longer thereby increasing the possibility of further particle addition and growth.

High values of fluidising air flow rate (factor 6) also increase evaporation rates thereby enhancing the effects of temperature. The degree of attrition and separation within the bed is also increased resulting in breakage of weak solid bonds within an agglomerate, leading to disaggregation. Lower flow rates reduce evaporation and attrition.

The two remaining factors 4 (temperature of granulating solution) and 5 (height of nozzle above distribution grid) also exert an effect although of less significance.

The temperature of the granulating solution has two effects. Viscosity is decreased with increased temperature thus improving the liquid flow and atomisation with a subsequent increase in droplet population. This is counteracted by the increased evaporation rate although when in contact with the atomising air the liquid temperature will be reduced by evaporative cooling with a corresponding decrease in evaporation rate.

Several authors (Johnson et al, 1975; Mobüs, 1969; Thurn, 1970) have found that the nozzle height has no effect. Evidence from this work does however suggest a very slight influence upon granule quality. At a large distance from the distribution plate there is a greater possibility of droplet evaporation prior to collision resulting in a reduction in the number of successful collisions. As the nozzle is moved closer to the bed the droplet /particle impact time is shortened , (as is the degree of evaporation.)

Two-Factor Interactions

The significant two-factor interactions are listed in Table 3.16. This shows that eight of these combinations have a significant effect on granule quality. In this case two divisions were discernable. Since the 'F'-ratios of these groups are similar in magnitude to divisions IIA and IIIA in Table 3.15, they are referred to as divisions IIB and IIIB respectively.

The interactions indicate the importance of keeping a high level of moisture in the bed since four of the five interactions in division IIB contain nozzle combination as one of the factors, whilst the other contains concentration (therefore volume) of granulating solution. The other variables in these two-factor interactions are all associated with evaporation rate or increased rate of granulating solution addition to the system. This supports the proposed mechanism of granule build up previously used to explain the single factor effects.

Table 3.16 Significant two-factor variables arranged in rank order of mean 'F' ratio (from Table 3.12).

DIVISION	INTERACTION	VARIABLES	MEAN 'F' RATIO
	2 + 6	nozzle combination/fluid air flow rate	44.2
IIB	2 + 3	nozzle combination/atomising air pressure	21.9
	1 + 2	concn. granulating soltn./ nozzle combination	14.7
	2 + 7	nozzle combination/fluidising air temp.	14.7
	1 + 7	concn. granulation soltn./ fluidising air temp.	10.8
	1 + 6	conc. granulating soltn./ fluidising air flow rate	5.9
IIIB	3 + 5	atomising air press./nozzle height above distribution grid	5.8
	6 + 7	fluidising air flow rate/ fluidising air temp.	5.8

The interactions in Division IIIB have a lower magnitude of significance on granule quality. All three mechanisms are again associated with quantity of moisture and evaporation rate. It is interesting to note that one of the interactions contains factor 5 (nozzle height above distribution grid) which some authors had previously thought not to have an effect.

Conclusions

The process variables found to exert a significant effect upon granule quality were those which affected the wetness of the powder mix and duration of drying during the granulation stage. The process conditions which will lead to the production of a 'good' granulation are:

a) a large spray nozzle combination which adds the solution at a faster rate.
b) a greater spray volume of granulating solution, i.e. a dilute solution of binder.
c) a lower fluidising air temperature and flow rate.
d) a low atomising air pressure which produces larger droplets of granulating solution.

The results of the experiment of factorial design that have been reported in this Chapter enabled those factors which exert a significant effect on granule quality to be identified and quantified statistically. The overall conclusions show that the wetting of the powder in the bed is a very significant stage in the granulation step in a fluidised bed. The absence of shear in an FBG make this stage even more important. This conclusion led this work to extend in two directions: a study of spray characteristics and droplet size (this is reported in Chapter 4) and also an investigation into how the hydrophobicity of the powder affects the wetting stage (reported in Chapter 5).

CHAPTER 4

SPRAY DROPLET CHARACTERISATION

CHAPTER 4

SPRAY DROPLET CHARACTERISATION

4.1 INTRODUCTION AND SCOPE OF CHAPTER

In the previous chapter, the effect that changes in the process variables had upon the properties of the granules produced in a fluidised bed was reported. From this it was concluded that the wetting of the granules was an important factor in such granulations. This lead to the work progressing in two directions in order to assess more fully this dependence. Firstly the droplet spray itself was characterised and secondly, the influence of the hydrophobicity of the powder was examined. The first of these studies is reported in this Chapter.

The work was divided into three sections. These consisted of an examination of the influence of the following spray droplet characteristics

i) Air atomisation pressure

ii) Process variables. Of the process variables examined previously in Chapter 3, four were directly related to the spray itself. These were:

1) The concentration (volume) of granulating solution.
2) The spray nozzle set-up.
3) The atomising air pressure.
4) The temperature of the granulating solution.

The effect of changes in these variables on the spray was studied in an experiment of 2^4 factorial design, using the same experimental values as defined in Chapter 3 (see Table 3.5).

iii) The addition of sodium lauryl sulphate to the spray. The aim of this was to observe the effect of adding a surfactant to the system in an attempt to improve the wetting of the powder by the granulating solution. This aspect of the work is discussed fully in Chapter 5.

The sprays were characterised by determination of the following properties.

a) droplet size distribution

b) spray addition rate

c) spray cone angle

d) length of cone before break-up.

Additionally, in each section the relationship between the spray characteristics and granule quality was investigated.

4.1.1. Methods of Spray Characterisation

The spraying of liquids is utilised in a widespread range of operations as a means of accelerating some physical or chemical process (Hasson and Mizrahi 1961). Familiar examples are to be found in operations such as spray drying, combustion, adsorption and humidification (Charlesworth & Marshall, 1960; Hesketh, 1973; Bradley, 1975; Bellomo, 1974; Eisenklam, 1961).

In order to optimise the use of atomised droplets in these various applications it is necessary to know the fundamental characteristics of a spray system. These fundamental characteristics which can be observed or measured for an atomised system in a practical application are:-

i) disintegration process

ii) atomisation angle

ii) spatial distribution of flow rate and the aerodynamic conditions

iv) distribution of droplet size, number-diameter, surface, volume, weight and their cumulative distributions

v) mean diameter

vi) other characteristic diameter i.e. median, mode, maximum and minimum.

In pharmacy the measurement of droplet size distribution of atomised sprays has been confined mainly to aerosol inhalations. Research into the process of fluidised bed granulation has neglected the effect of the spray droplet distribution upon the build up of particles within the bed. This has probably been due to the extreme difficulty in accurately measuring the size of the droplets from the atomised granulating solution. The initial drop size distribution created at the first moment of break-up may change along the distance of travel which further adds to the problem. It may also be altered during the sampling and sizing operations during measurement.

Droplet Size Determination

Droplet sizing techniques can be broadly classified into three basic categories: captive techniques, direct photography and optical methods.

Initially in this work a captive technique was employed since it is the most common method for droplet measurement. There are several techniques for droplet collection and these include air elutriation, centrifugation, thermal precipitation, electrostatic precipitation, sedimentation and impaction (McGreath and Beer, 1976). Analysis after collection is by either counting (using optical or electron microscopy), weighing or other means. The simplest and most commonly used method is by droplet capture which involves droplet impingement upon glass microscope slides or vessels containing oils (Nukiyama and Tanasawa, 1938; Fraser and Eisenklam, 1956; Golitzine, 1951; Thurn 1970). Magnesium oxide coated glass plates have also been used (Dixon, 1959). The captured sample can then be analysed for number and size of droplets.

Collection of a suitable sample of droplets is obtained using a shutter. Nukiyama and Tanasawa (1939) employed a cylindrical shutter whilst Gunn-Smith and Platt (1961) used a vertical shutter device. These shutters are important since if the number of droplets collected is too large then the mean diameter of the spray becomes larger due to collision and combination of the droplets. Problems also occur during collection since the physical presence of the collecting apparatus (slide or vessel) does change the aerodynamics of the systems which in effect changes the trajectory of the atomised droplets. The work of Langmuir and Blodgett (1946), and subsequently confirmed by Geist et al (1951), has shown that such sampling processes do discriminate against the capturing of the smaller droplets.

The direct methods of spray analysis are in general very time consuming and sometimes inaccurate with inherent errors due to collection of unrepresentable samples, evaporation problems, coalescense and flattening of the droplets (Golitzine, 1951). Consequently after the initial work with the shutter and impingement device described in section 4.2.2a, more accurate and quantitative measurements were carried out using the Malvern Instruments ST 1800 Particle and Droplet Size Analyser (section 4.2.3). This method is a simple and

rapid technique which can examine a large number of drops simultaneously. A laser beam is shone into a cloud of drops and the light energy, diffracted into small forward angles, is measured by means of a photo detector array. The droplet size distribution can be calculated from the energy distribution in the array. The basis of the technique depends on the angular intensity distribution, $I(\emptyset)$, of light diffracted by a sphere of radius a, at small forward angle $\emptyset$ is described by

$$I(\emptyset) = I_o \left[\frac{2J_1 \left(\frac{2\pi a}{\lambda} \theta\right)}{\left(\frac{2\pi a}{\lambda} \theta\right)} \right]^2$$

where I_o is the incident beam intensity

J_1 is the first order Bessel function

a is the particle radius

and λ is the wavelength of the light

This light distribution appears as a series of concentric alternating light and dark rings on a screen. The rings appear at different positions for drops of different sizes, thus when several different sized drops are present a summed light distribution is obtained. From this distribution it is possible to extract the drop size distribution.

4.1.2 Drop Size Analysis

Drop counting methods result in a drop size distribution giving the number of drops within suitable group sizes. The analysis of these distributions to obtain parameters, such as mean and dispersion, has not been satisfactorily solved due to the difficulty caused by the variability of the actual size distributions obtained (Fraser & Eisenklam, 1956). The two means most commonly used are the median and the surface mean diameter. The former is defined as that diameter above or below which lies 50% of the number or volume of the drops. This value can be directly obtained from cumulative percentage curves of the distribution. The surface mean diameter or Sauter Mean Diameter is defined as the diameter of a drop which would have the same surface to volume ratio as that of the total spray.

Many size distribution functions have been proposed which define the actual distribution to a mathematically derived function. These

distribution functions, which are often used for practical and research purposes, are empirical in nature and depend upon the mechanism of disintegration. Several of these distribution functions are frequently used to describe droplet size distributions in sprays. These include Nukiyama-Tanasawa (1938 and 1939) number distribution, the log number distribution (see Claire and Radcliffe, 1954), the log normal number distribution and Rosin-Rammler distribution (1933).

However not one of the distribution equations can accurately describe the actual dropsize distribution over a sufficiently wide range. Thus the selection of a function to describe the distribution of a particular spray depends on that function's ability to fit the actual data.

It has been concluded by Mugele and Evans (1951) who examined the results of nine different investigators that the Rosin-Rammler distribution fitted the available spray data better than two other distributions and was only marginally bettered in accuracy by the upper limit log normal distribution, a three parameter distribution. Later photographic work on drop sizing has confirmed the suitability of the Rosin-Rammler distribution in twin fluid atomisers (Fraser et al, 1963). These atomisers are used in fluid bed granulation.

4.1.2a Rosin-Rammler Distribution

The Rosin-Rammler distribution (Rosin and Rammler, 1933) is defined such that the weight, or volume, fraction of particles or droplets, larger than size x is given by R; where:

$$R = e^{-(x/\bar{x})^W}$$

Conversely, the cumulative fraction can be expressed as:

$$1 - R = 1 - e^{-(x/\bar{x})^W}$$

$\bar{x}$ is the Rosin-Rammler mean particle size.

The notation $\bar{x}$ is a characteristic size where it can be seen that a weight (or volume) fraction 1/e (= 0.368, i.e. 36.8%) is larger than $\bar{x}$ and 0.632 (63.2%) of the particles or droplets are less than $\bar{x}$.

Thus $\bar{x}$ is the drop diameter above which lies 36.8% of the total spray volume. The dispersion factor (w) is a measure of the spread of the size distribution such that $w = \infty$ for a mono-dispersed size distribution, and $1.5 < w < 4$ for most liquid/air spray nozzle systems. The higher the value of this dispersion coefficient, the narrower the distribution.

4.2. METHOD

4.2.1 Introduction

As indicated previously (section 4.1.1), there are many methods available for droplet size analysis. In this work, the initial aim was to make qualitative comparisons between the sprays in order to assess if there were indeed significant changes in spray characteristics as a result of changes in the four factors previously listed. Then, if this was so, to carry out an accurate, quantitative determination of the droplet size distribution in order to correlate spray properties with the properties of the resulting granules.

4.2.2 Qualitative Spray Evaluation

Three methods of obtaining a permanent record of the spray produced were considered:-

(i) Adding a small amount of soluble dye to the granulating solution and spraying onto semi-absorbent paper. This was not considered suitable since it was thought that the dye may affect the surface tension of the granulating solution and thus the formation of droplets.

(ii) Using alcohol sensitive paper as the recording medium and adding alcohol to the granulating solution. In addition to the problem of the alcohol affecting the physical properties of the granulating solution i.e. surface tension and subsequently droplet size, there was also the added problem of evaporation during spraying.

(iii) Finally it was decided to use smoked paper on the assumption that each droplet would displace an amount of carbon which would be some function of its size. This would leave the white surface of the paper underneath as an approximate record of the droplet size. The paper could then be fixed by varnishing to give a permanent record.

It must be emphasised of course that this final method will produce a record, the size of which will not be equal to, but will be some function of, the size of the droplets. It is appreciated that this method can only be used for rough qualitative comparisons.

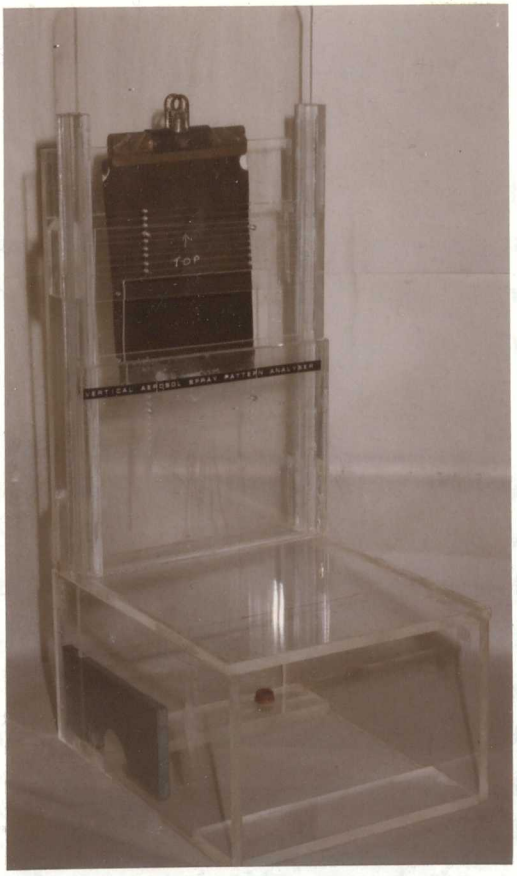
4.2.2a Vertical Spray-Analyser

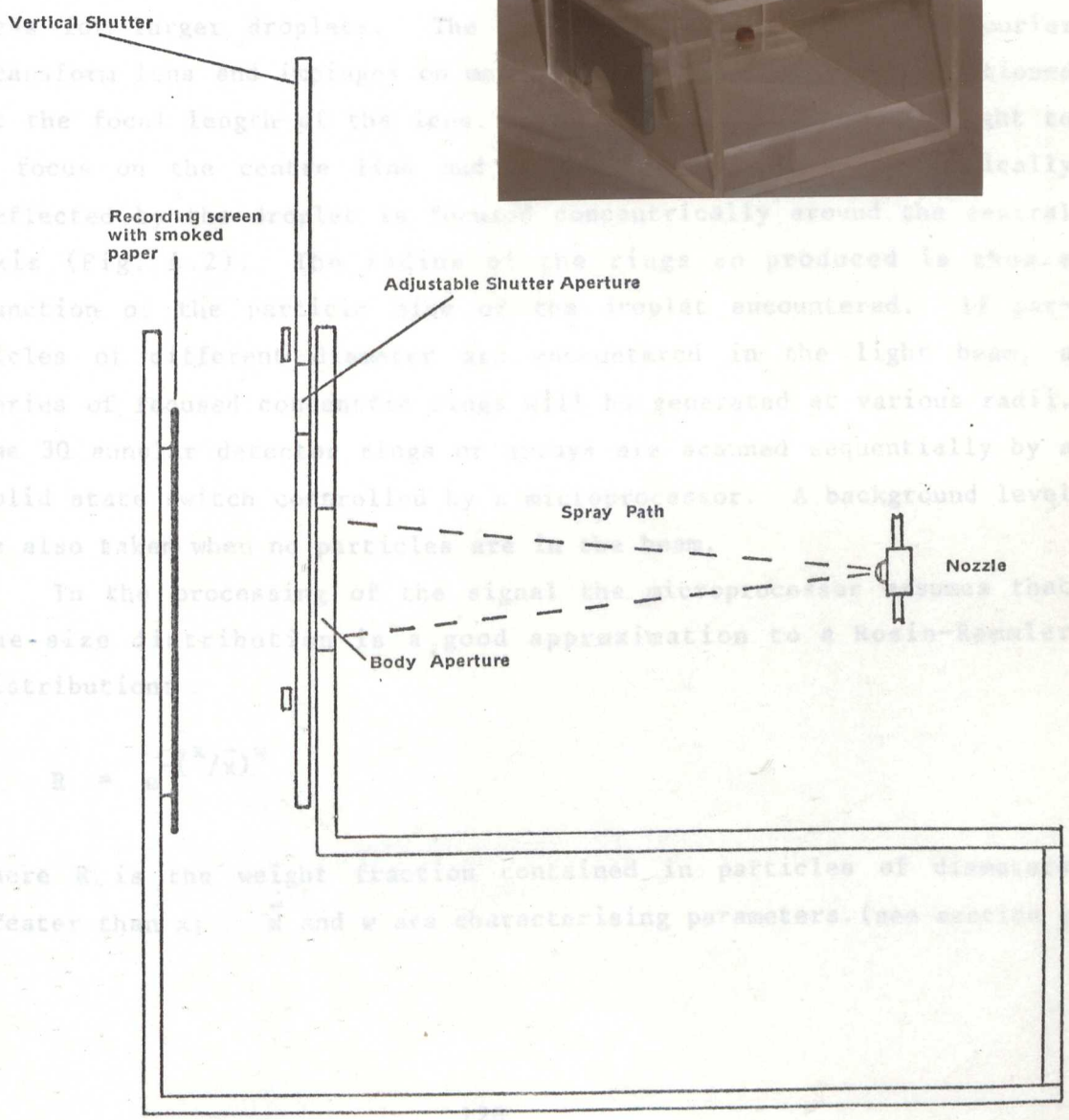
In order to be able to observe discrete drops on the recording paper, it was necessary to sample the spray for a very short time. This was achieved by the construction of a vertical spray-analyser based upon the design of Gunn-Smith and Platt (1961). This is shown in Fig. 4.1. It is constructed of perspex and consists of a body, frame, shutter with aperture and a recording screen. The nozzle under test is clamped at the required distance from the recording screen. At the rear of the body there is a vertical frame which accepts the easily removable paper, thus acting as the recorder screen. The vertical shutter device is capable of free fall under gravity guided by vertical grooves in the frame and is positioned so that it passes through the test spray. The nozzle is aligned such that its spray passes through the shutter by way of a horizontal adjustable aperture. This adjustable aperture allowed the exposure time to be varied enabling a variety of sampling times to be accommodated.

4.2.2b Procedure

A piece of paper was smoked over a benzene flame and placed on the recording screen. The spray nozzle was positioned 200 mm away from the spray wall. The slot width on the shutter was set at 100 mm, as determined by previous experiments. The shutter was raised into a position whereby its lower half protected the smoked record paper from the spray. The spray was allowed to stabilise at the pre-set run conditions and the nozzle was pointed horizontally and aimed at the record paper. The shutter was allowed to fall by gravity enabling the spray to come into contact with the smoked paper as the aperture passed through the spray field. The smoked paper was then carefully removed, "fixed" by varnishing and allowed to dry.

Fig. 4.1 Vertical Spray-Analyser





This procedure was repeated for all spray combinations and the permanent records obtained could then be handled without damage during analysis.

4.2.3 Malvern Instruments ST 1800 Particle and Droplet Size Analyser .

Until recently it has been difficult to accurately, easily and quickly measure spray droplet size disribution. However, the Malvern Instruments ST 1800 Particle and Droplet size analyser, using the technique of Swithenbank et al (1976), has been used successfully in this work.

In the Malvern analyser a parallel beam of monochromatic light (He/Ne, λ = 632.8 nm) is shone across a distance of about 1 metre. The spray is then shot through this beam. When the light falls on a droplet some of it is deflected by an amount depending on the size of the particle; the diffraction angle is large for small droplets and less for larger droplets. The light then passes through a Fourier transform lens and impinges on multi-element detector rings positioned at the focal length of the lens. The undeflected light is brought to a focus on the centre line and the light which has been conically deflected by the droplet is focused concentrically around the central axis (Fig. 4.2). The radius of the rings so produced is thus a function of the particle size of the droplet encountered. If particles of different diameter are encountered in the light beam, a series of focused concentric rings will be generated at various radii. The 30 annular detector rings or arrays are scanned sequentially by a solid state switch controlled by a microprocessor. A background level is also taken when no particles are in the beam.

In the processing of the signal the microprocessor assumes that the size distribution is a good approximation to a Rosin-Rammler distribution:

$$R = e^{-(x/\bar{x})^w}$$

where R is the weight fraction contained in particles of diameters greater than x; $\bar{x}$ and w are characterising parameters. (see section 4.1.2.a)

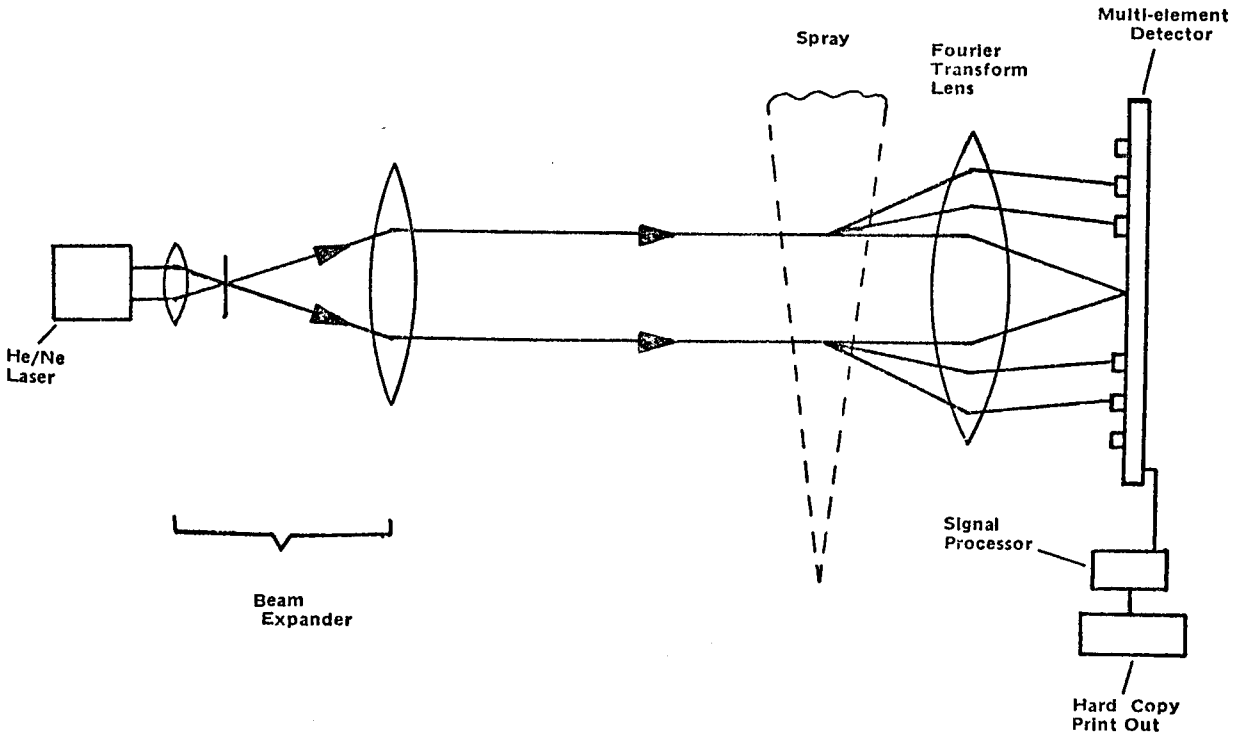


Fig. 4.2 Schematic Diagram of Malvern ST 1800 Particle and Droplet Size Analyser

The number of calculation iterations can be reduced if initial estimated values of $\bar{x}$ and w are selected by the operator. The weight fraction distribution is by using through the above equation. The energy distribution corresponding to this Rosin-Rammler distribution is calculated and compared with the experimentally obtained energy distribution. The parameters $\bar{x}$ and w are then optimised to give the best fit. This is carried out by a computer incrementally increasing w in 0.1 steps, optimising the $\bar{x}$ value, and printing out the error (the sum of squares of the differences between the calculated and measured energy distributions). This calculation is repeated until a minimum is detected in the error. The programme then fixes on the appropriate $\bar{x}$, w values, and the Rosin-Rammler distribution corresponding to those parameters is typed out.

The accuracy and limitations of obtaining reliable results using Malvern measurement technique have also received comment. However, the work of Negus and Azzopardi (1978) refuted any criticism since their results from the Malvern Analyser were in good agreement with those determined from photographic analysis. They concluded that the results were also unaffected by the refractive index and transmission of the particles.

4.3 EXPERIMENTATION

4.3.1 Effect of Atomising Air Pressure

The effect of changing the atomising air pressure upon the droplet size distribution of an atomised, 5% $^{w}/_{v}$ PVP solution was investigated using a pressure spray system (see section 2.2.2). Results in section 3.4 indicated the atomising air pressure affected granule quality. The aim of this experiment was to quantify the effect of the atomised air upon the droplet distribution of the spray and ultimately correlate this with granule quality.

Pressure system No. 11 as described in Table 2.2 was set up with the nozzle clamped and directed such that the generated spray would pass through the laser beam of the Malvern instrument. The distance between the tip of the nozzle and the beam was set at 200 mm. This is equivalent to the distance in the FBG between the spray nozzle and the surface of the fluidised powders at an air flow rate of $25 \times 10^{-3} m^3 s^{-1}$. A 5% $^{w}/_{v}$ aqueous PVP solution, at 20°C was sprayed at a liquid pressure of 1.4 bar and an air atomisation pressure of

1.17 bar. The spray was allowed to stabilise for 15 seconds and a reading taken. This procedure was repeated using atomising air pressures of 1.33, 1.67 and 2 bar.

4.3.2 2^4 Analysis of Spray Droplet Distribution Size

The results of the analysis of the 2^7 experimental data (section 3.4) showed that the spray nozzle and therefore droplet size had a significant effect upon the physical properties of the granules produced. Of the seven variables assessed four had an effect upon the spray and therefore the Malvern apparatus was used to measure differences in droplet size distributions produced by changes in these variables in a 2^4 factorially designed experiment. The values used are listed in Table 4.1 and are identical to those in Chapter 3.

Table 4.1. Values of variables used in the 2^4 Analysis of droplet size distribution

Code No.	Variable	Value	
		-	+
1	Concentration Granulating Solution	5% $^{w}/_{v}$	10% $^{w}/_{v}$
2	Spray Set Up*	1*	2*
3	Atomising Air Pressure	1.67 bar	2.67 bar
4	Temperature Granulating Solution	30°C	60°C

* See table 2.1

4.4. RESULTS

4.4.1 Qualitative

A review of the smoked drum records indicated that there were indeed differences between the sprays generated by changing values of the four variables under investigation. These differences are illustrated in Fig. 4.3. These clearly show the individual drops impinged on the smoked drum records. Evaluation of these records was achieved by photographic enlargement; a typical example of such is shown in Fig. 4.4.

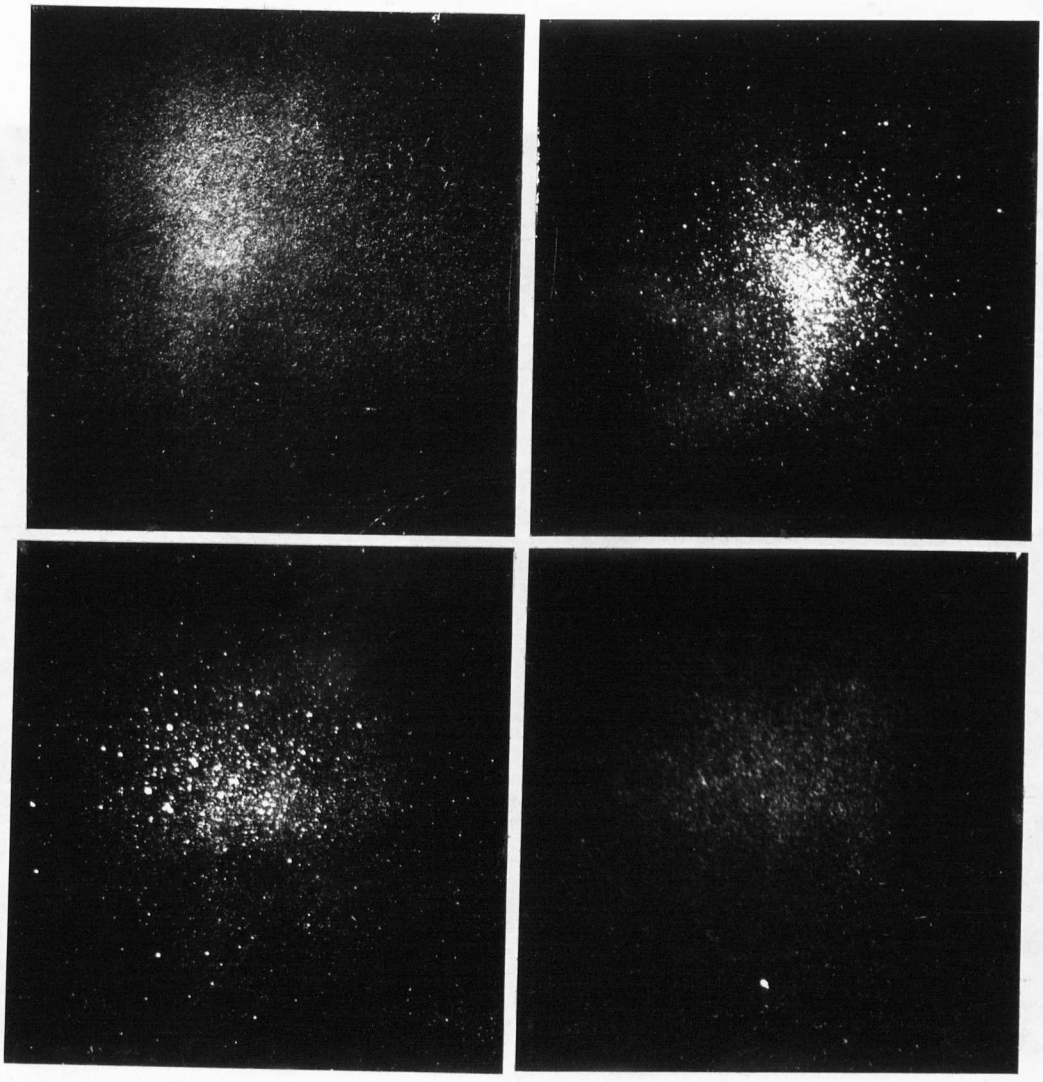


Fig. 4.3 Photographs of Smoked Drum Records
(actual size)

Fig. 4.4 Photographic Enlargement of a Smoked Drum Record (magnification x8)

The method even though qualitative in nature was useful since it did show differences between the sprays and emphasised the necessity for continued investigation of the droplet size and distributions by a more accurate technique. This was achieved with the Malvern ST 1800 Particle and Droplet Size Analyser.

4.4.2 Malvern Results

4.4.2a Effect of Atomising Air Pressure on Droplet size Distribution.

A 5% $^{w}/_{v}$ solution of PVP was pumped into the spray nozzle at 1.17 bar. Measurements of droplet size distribution were taken at various atomising air pressures ranging from 1.17 to 2 bar. The following results were obtained (Table 4.2).

Table 4.2. Summary of Droplet Size Distribution with Atomising Air Pressure

Run No.	Air Pressure (bar)	$\bar{x}$ (μm)	w
4	1.17	95	2.0
3	1.33	59	1.8
2	1.67	30	1.6
5	2	15	1.8

It can be seen that there is little change in the width of the distribution, but that there is a marked difference in the mean droplet size which fellfrom Rosin-Rammler mean of 95μm at 1.17 bar to 15μm at 2 bar air pressure. This is clearly shown in Fig. 4.5 and 4.6 which show the weight fraction and cumulative weight fraction distribution respectively.

4.4.2b 2^4 Results

(i) Results of Changing Process Variables on Spray Characteristics.

The particle size distributions for each of the 16 experiments in this section are shown in Figs. 4.7a to 4.7d.

In order to assess the influence of changing process variables a qualitative treatment was used initially. This was done by arranging the results in rank order of Rosin-Rammler mean ($\bar{x}$) in Table 4.3, Rosin-Rammler Dispersion Coefficient (w) in Table 4.4 , and spray rate (Table 4.5). These tables enabled any obviously significant effects to be observed; such trends were later confirmed statistically. Alongside each run number in the tables is written the variable code (i.e. + or −, see Table 4.1); an abundance of either of these symbols at any one end of a column of the table shows a tendency for that factor to have a significant effect on the spray property being evaluated.

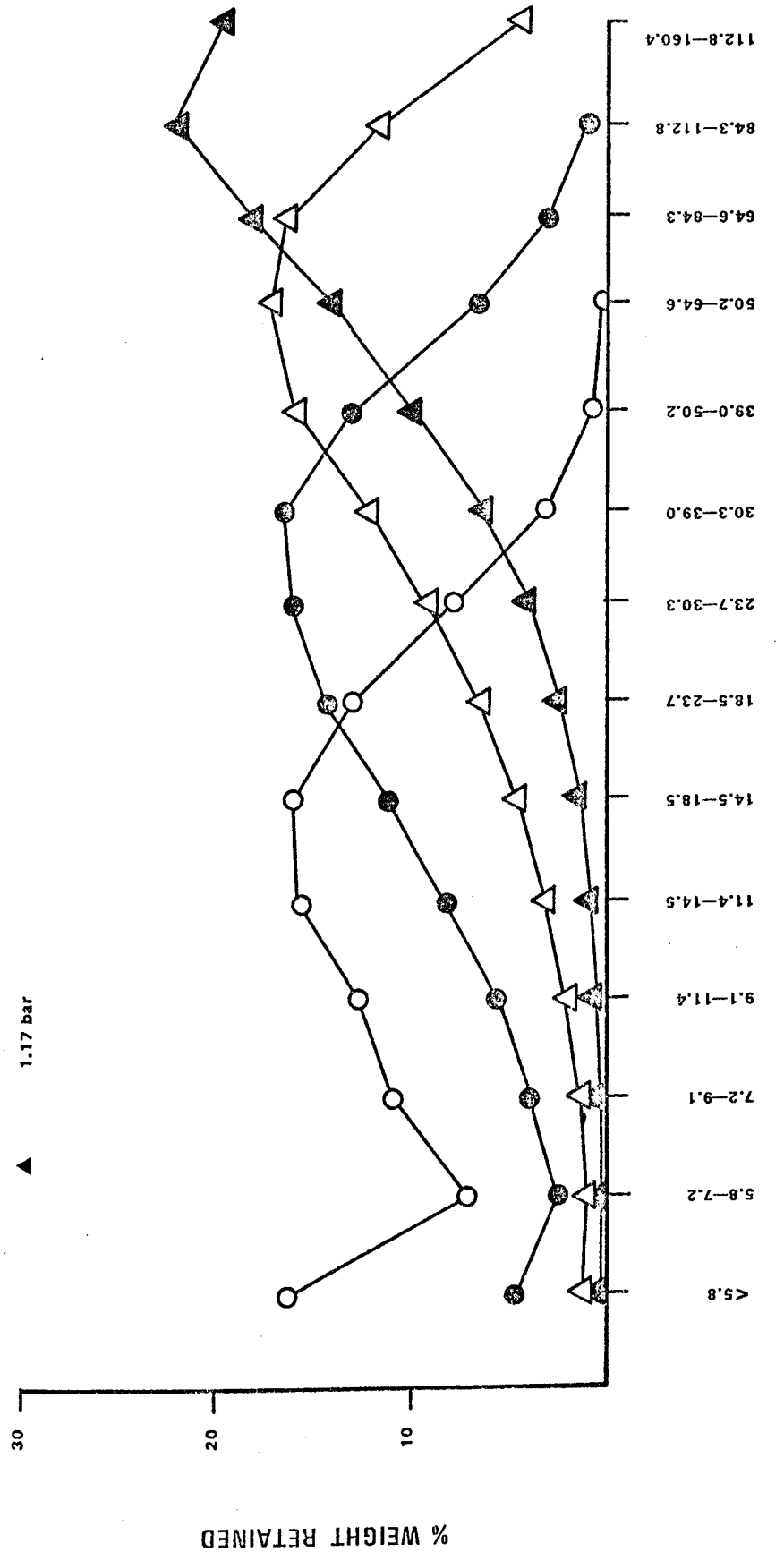


Fig. 4.5 Effect of Atomising Air Pressure on Droplet Size Distribution

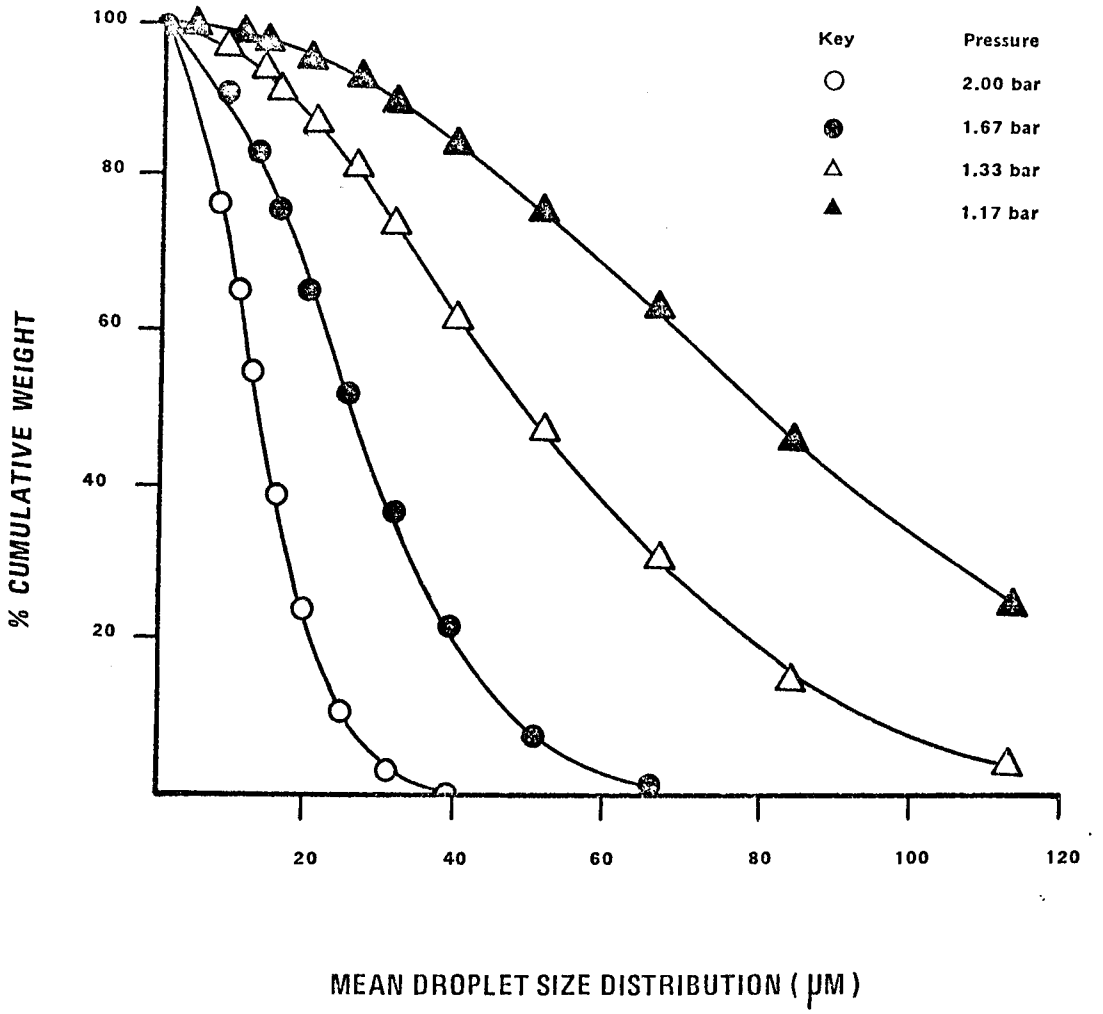


Fig. 4.6 Effect of Atomising Air Pressure upon Cumulative Droplet Size Distribution

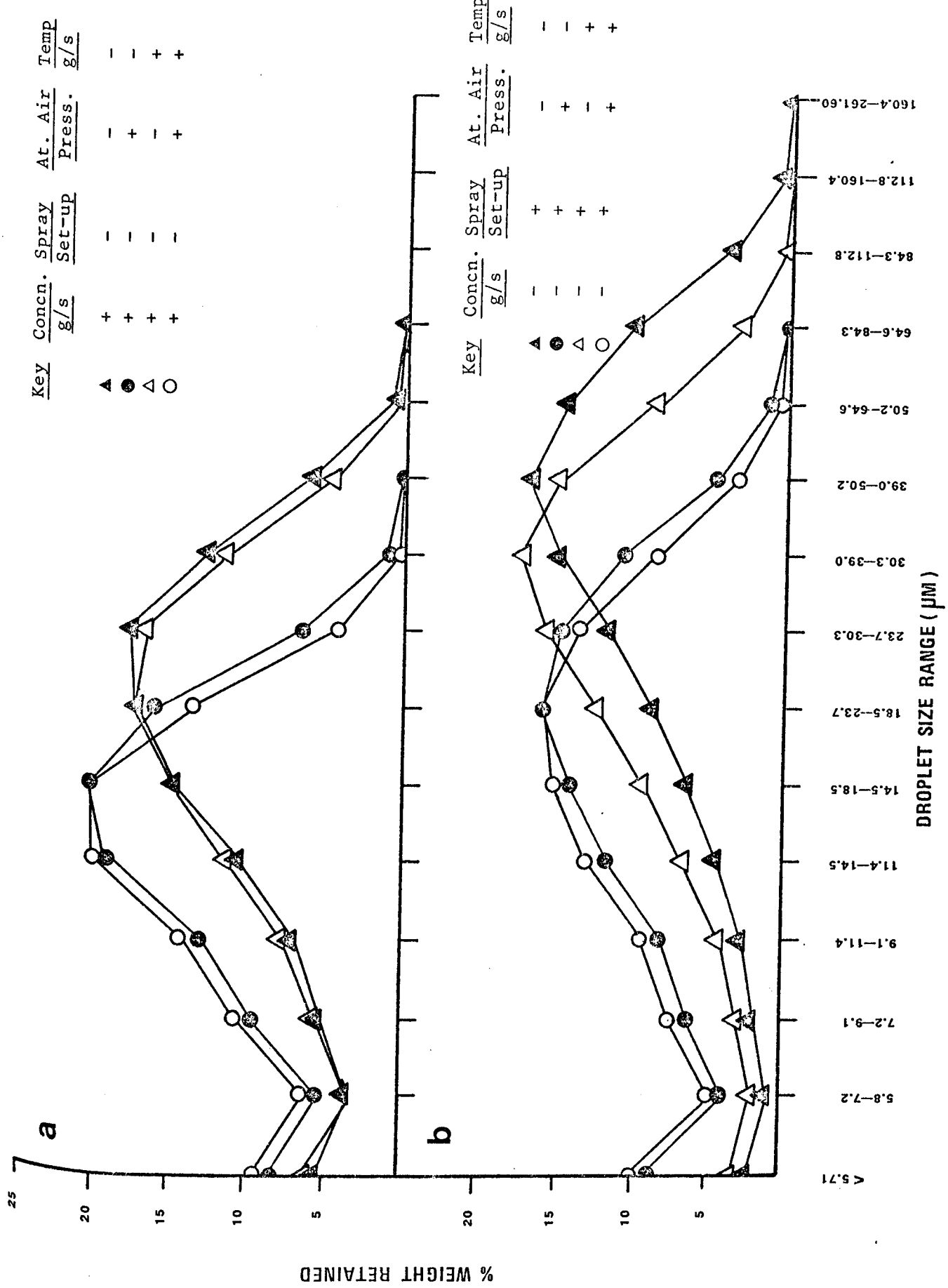


Fig. 4.7a-b Effect of changing Process Variables upon Droplet Size Distribution (For value represented by Key, see Table 4.1)

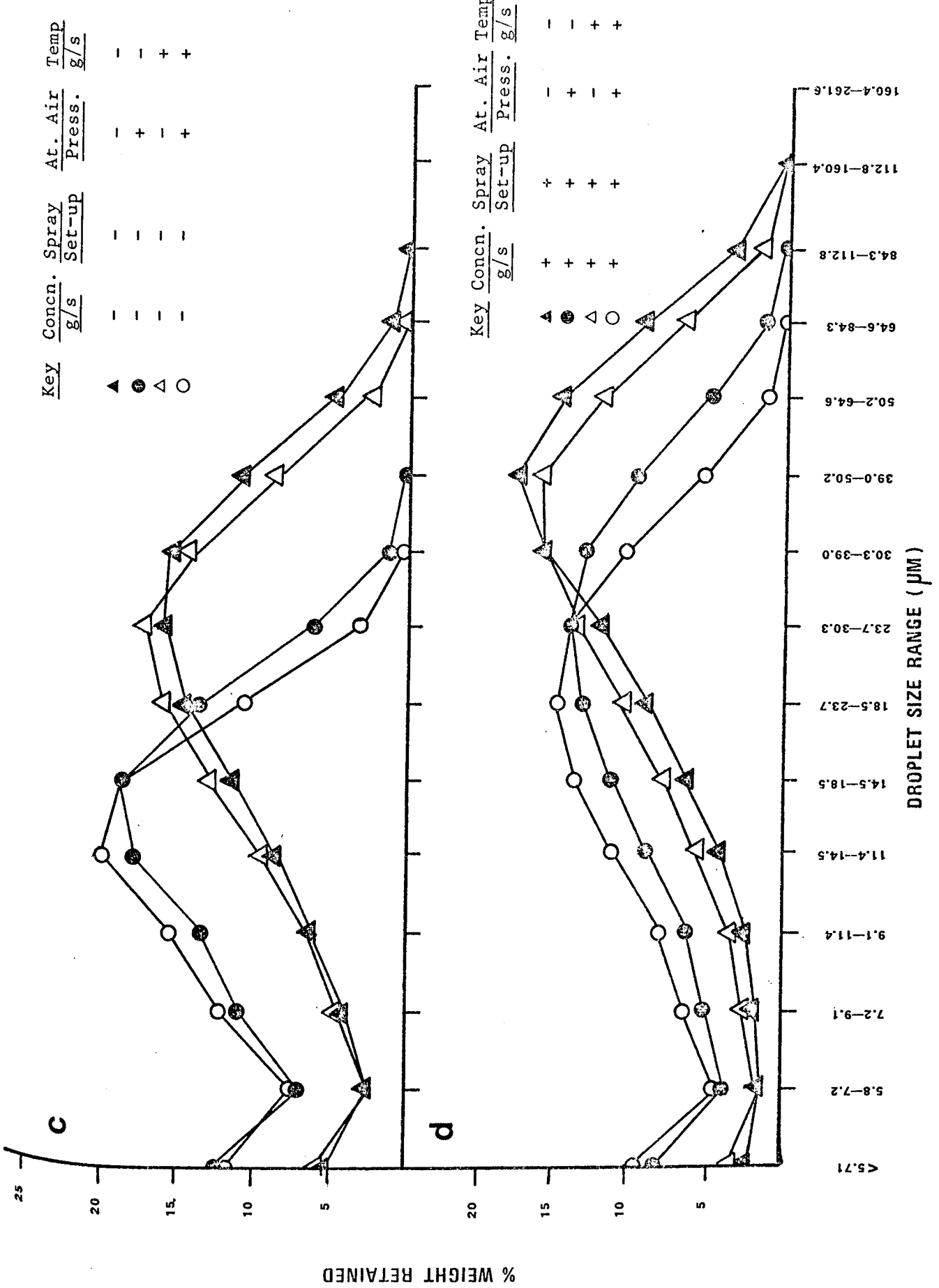


Fig. 4.7c-d Effect of changing Process Variables upon Droplet Size Distribution (For value represented by Key, see Table 4.1).

Table 4.3. Table of Rosin-Rammler mean ($\bar{x}$) in rank order together with variable format code.

Malvern Run No.	$\bar{x}$ (μm)	Concn. Gran. Soltn.	Spray Set Up	Atom-ising Press.	Temp. Gran. Soltn
29	45	-	+	-	-
33	44	+	+	-	-
35	39	+	+	-	+
31	34	-	+	-	+
21	28	-	-	-	-
34	27	+	+	+	-
23	26	-	-	-	+
25	24	+	-	-	-
27	23	+	-	-	+
30	22	-	+	+	-
36	22	+	+	+	+
32	20	-	+	+	+
26	16	+	-	+	-
22	15	-	-	+	-
28	15	+	-	+	+
24	14	-	-	+	+

Examination of the results in Table 4.3 for the Rosin-Rammler mean droplet size, shows that two of the variables examined had an effect on this value. The four + values at the top of column 2 and the four - values at the bottom of that column suggest that the spray set up has a significant effect upon droplet size i.e. the four runs with the largest droplets were produced by spray set up "2" (manufacturers code see Table 2.1) and the four finest sprays were all produced by the smaller spray set up "1".

Atomising air pressure also appeared to have a significant affect; the larger droplets being produced by the lower air pressure (as found previously in section 4.4.2a).

The other two factors (concentration and temperature of granulating solution) appeared from the approximately random distributions of + and - to have little or no effect on droplet size.

Table 4.4. List of Rosin-Rammler distribution w in rank order together with variable format code.

Malvern Run No.	w	Concn. Gran. Soltn.	Spray Set Up	Atom-ising Press.	Temp. Gran. Soltn.
26	2.4	+	-	+	-
28	2.4	+	-	+	+
24	2.3	-	-	+	+
22	2.1	-	-	+	-
27	2.0	+	-	-	+
25	2.0	+	-	-	-
23	1.9	-	-	-	+
33	1.9	+	+	-	-
31	1.9	-	+	-	+
21	1.8	-	-	-	-
29	1.8	+	+	-	-
35	1.8	+	+	-	+
30	1.8	-	+	+	-
32	1.8	-	+	+	+
36	1.7	+	+	+	+
34	1.6	+	+	+	-

Table 4.4. lists the results in rank order of the Rosin-Rammler dispersion coefficient, w. From visual observation it appears that variable 2 (spray set up) and 3 (atomising air pressure) again have a significant effect, whereas variable 1 (concentration gran. soln.) and 4 (temp. gran. soln.) do not.

The large spray set-up (+ in column 2) produced a wider distribution of droplet sizes (i.e. smaller w) than the smaller spray set-up. The effect that atomising air pressure had upon the width of the distribution is rather complicated since a diversity of effect is indicated from Table 4.4.. The high atomising air pressure not only produced the sprays with the widest distribution but also those with the narrowest distribution of droplet size. The lower atomising air pressure produced size distributions of an intermediate width. These somewhat contradictory results are probably due to:-

(a) the use of two different spray nozzle units resulting in
(b) different nozzle discharge rates of granulating solution caused by the siphon effect of the atomising air pressure.

Hence for low discharge rates more energy would be available for liquid to droplet break up whilst at high rates the degree of break-up would be less efficient. In fact for nozzle combination "1" there is a w range of 0.6 and for combination "2" this range is only 0.3. This indicates that for combination "2" the droplet distributions are similar. In fact this is reflected in four combinations having the same w value.

Table 4.5. Table of addition rate of granulating solution in rank order together with droplet size.

Malvern Run No.	Spray Rate Droplet Size			Concn. Gran. Soltn.	Spray Set Up	Atom-ising Press.	Temp. Gran. Soltn.
	ml min^{-1}	$\bar{x}$	w				
32	73	20	1.8	-	+	+	+
30	70	22	1.8	-	+	+	-
34	64	27	1.6	+	+	+	-
36	64	22	1.7	+	+	+	+
31	51	34	1.9	-	+	-	+
29	48	45	1.8	-	+	-	-
33	42	44	1.9	+	+	-	-
35	42	39	1.8	+	+	-	+
24	19	14	2.3	-	-	+	+
26	18	16	2.4	+	-	+	-
22	17	15	2.1	-	-	+	-
28	16	15	2.4	+	-	+	+
23	11	26	1.9	-	-	-	-
21	9	28	1.8	-	-	-	-
27	8	23	2.0	+	-	-	+
25	7	24	2.0	+	-	-	-

Table 4.5 lists these different spray rates in rank order and it can be concluded that spray set up and atomising air pressure also had a significant effect on liquid throughput of the nozzle. The faster spray rates were produced by the larger spray set up and the higher atomisation pressure.

(ii) Yates' Analysis of the Results

The conclusions drawn above are only tentative in that they were made by visual observation of a simple rank-order technique. It is possible, however, to quantify the significance of these effects by the statistical method of Yates. This analysis also enables multi-factor effects to be observed. A complete description of this method has previously been given in section 3.4.2. The results of such an analysis in terms of F-ratios and significance levels, are shown in Table 4.6 for the mean droplet size ($\bar{x}$), size dispersion coefficient (w) and spray rate results.

The results from Yates analysis support the conclusions derived from an examination of Tables 4.4, 4.5 and 4.6. Granulating solution concentration and temperature also were shown to have a significant effect upon flow whereas this had not been shown from visual assessment of Table 4.5. It may also be surprising that certain multifactor relationships do not appear to be significant (e.g. multifactor 1 + 3) but this may be explained by each factor exerting an equal but opposite effect.

4.5. DISCUSSION AND CONCLUSIONS

4.5.1 Effect of Atomising Air Pressure

The effect of atomising air pressure upon droplet size has been shown in Table 4.2 to manifest itself in a reduced droplet size distribution with increased atomising air pressure. This is due to the increased volume of air with a larger amount of energy available to break up the liquid. The mechanical function of the atomiser nozzle is to accelerate and disintegrate the liquid by the production of a liquid sheet from which threads and finally drops are produced, due to the surface tension of the liquid, together with dispersing the resulting drops. For any particular liquid, the drop size of the eventual spray has been shown (Fraser and Eisenklam, 1956; Matsumoto and Takashima, 1971) to be determined by the air to liquid ratio and the relative velocities, increasing as the air pressure and air to liquid ratio is reduced.

An attempt was made to investigate the relationship between the droplet size distribution of the spray and the quality of the final granulation formed in the fluidised bed. This assessment entailed preparing four lactose granulations under identical conditions, except for changes in the atomising air pressure to the nozzle, using the experimental values shown in Table 4.7 following the procedure

Table 4.6. Confirmation of Trends by Yates' Analysis

Variable	Rosin-Rammler Mean ($\bar{x}$)		Dispersion Coefficient (w)		Spray Rate	
	F-ratio	Significance Level	F-ratio	Significance Level	F-ratio	Significance Level
1. Concentration of Granulating Soltn.	0.67	-	2.5	-	264	0.001
2. Spray Nozzle Set-up	158	0.001	105	0.001	22,223	0.001
3. Atomising Air Pressure	234	0.001	15	0.025	2833	0.001
4. Temperature Granulating Soltn.	14.6	0.025	2.5	-	18.3	0.01
Significant Multifactor Effects						
1 + 2	-	-	15	0.025	110	0.001
1 + 4	-	-	-	-	18.3	0.01
2 + 3	16.8	0.01	62.5	0.001	533	0.001

Table 4.7 Optimised run conditions for each granulation to assess effect of atomising air pressure

Stage	Parameter	Value
Granulation	Weight of powder charge	750 g
	Volume of a 5% $^{w}/_{v}$ PVP granulating solution added	200 ml
	Fluidising air temperature	50°C
	Fluidising air flow rate	25 x 10^{-3} m^3 s^{-1}
	Nozzle height above distribution grid	445 mm
	*Manufacturers spray set up No.	11
	Atomising air pressures investigated	1.17, 1.33, 1.67, 2 bar
	Fluid addition pressure	1.4 bar
	Granulation solution temperature	20°C
Drying	Drying air temp.	65°C
	Drying air flow rate	30 x 10^{-3} m^3 s^{-1}
	Temperature granulation dried to	50°C

* See Table 2.2.

described in section 2.2.3. Each granulation produced was screened as outlined in section 2.4.1 to determine granule size distribution. Unfortunately changes in atomising air pressure, whilst affecting spray droplet size, also exerted a significant influence upon flow rate of liquid through the nozzle. This resulted in a wide variation in addition rate of liquid to the fluidised bed ranging from approximately 5ml min^{-1}

to 80ml min^{-1} and thus the evaluation primarily showed the effect of addition rate of liquid and not solely spray droplet size. The data from this evaluation showed that the large spray droplet size (high liquid addition rate) produced a larger mean particle size of granules. At the higher liquid addition rate (atomising air pressure of 1.17 bar) however, overwetting occurred in the bed with considerable oversize granule formation due to poor fluidisation with the final granule size data considered unsuitable for presentation.

In an attempt to isolate the effect of spray droplet size an additional investigation was performed and this is described in the following section.

4.5.1a Effect of Spray Droplet Size upon the quality of granules produced under standard conditions in the fluidised bed.

The object of this section was to investigate the relationship between spray droplet size and final granule quality. This was achieved by initially optimising conditions whereby atomisation could be varied without changing liquid flow rate through the nozzle. Once this was obtained the degree of atomisation was measured and then a number of granulations performed under identical conditions to assess spray droplet size upon final granule quality.

(i) Atomisation

After a number of experiments it was found that the degree of atomisation could be changed without affecting granulating liquid flow rate by using various air caps with a particular fluid cap. These combinations are shown in Table 4.8 along with Rosin-Rammler droplet size data after spray measurements using the Malvern ST 1800 Droplet Analyser (see section 4.3.1). The results indicate that as the diameter of the air cap orifice increases there is a corresponding reduction in droplet size. This is attributed to the increase in volumetric air flow rate which increases the proportion of air to liquid in the spray nozzle thereby improving atomisation. The particle size distribution data from the Malvern spray droplet analysis are displayed in Fig. 4.8a, b and c.

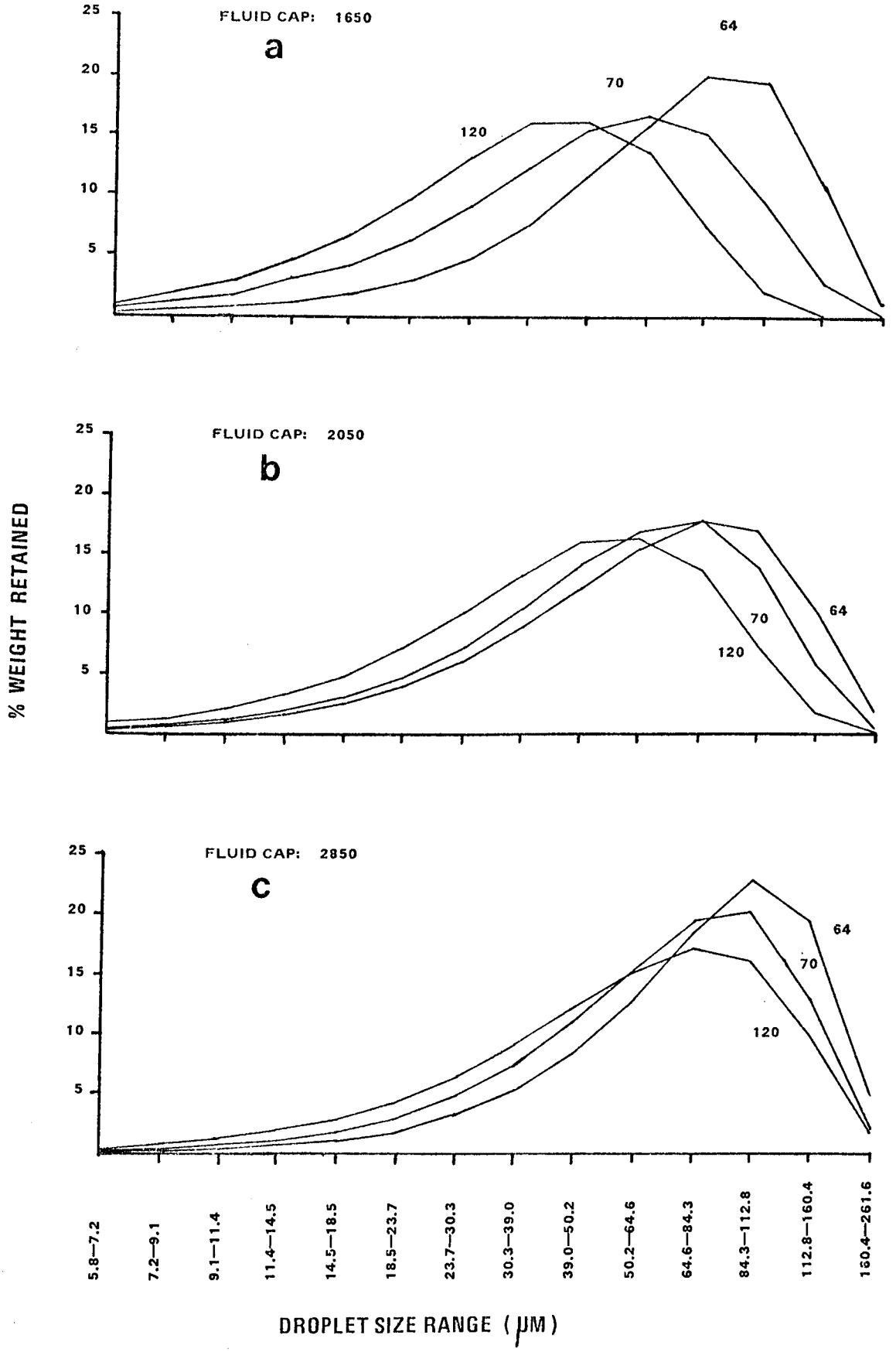


Fig. 4.8a-c Effect of Air Cap Changes on Droplet Size Distribution from Nozzles with Various Fluid Caps

Table 4.8 Summary of Droplet Size Distribution with various combinations of Fluid and Air Caps.

Fluid Cap Code	Air Cap Code	Addition Rate of Granulating Fluid ml min^{-1}	ROSIN RAMMLER DATA	
			Mean $\bar{x}$ (micron)	Distribution w
1650	64	53	79.1	2.11
1650	70	53	56.1	1.82
1650	120	53	41.1	1.86
2050	64	87.5	74.4	1.84
2050	70	87.5	65.5	1.89
2050	120	87.5	51.9	1.81
2850	64	170	95.8	2.16
2850	70	170	81.9	2.03
2850	120	170	73.3	1.76

(at an air pressure of 1.67 bar and liquid pressure of 1.4 bar)

(ii) Granulation

The effect of the three spray droplet size distributions for each spray rate (nozzle fluid cap variation) upon the granulation of lactose within the fluidised bed was assessed. Each granulation was prepared as described in section 2.2.3 under the conditions outlined in Table 4.7 using an atomising air pressure of 1.67 bar. Granulations manufactured for each of the air cap/fluid cap combinations were prepared identically in this way. The size distribution of granules from each granulation was determined by sieve analysis (see section 2.4.1). The relationship between mean particle size of granules and Rosin-Rammler mean spray droplet size are shown in Fig. 4.9. A linear relationship can be clearly seen indicating that a larger droplet size produces a larger granule size. This is due to a number of effects which can be explained by considering in more fundamental detail the role of the droplet of granulating solution during the collision with the powder particle(s). The large droplets have a relatively large

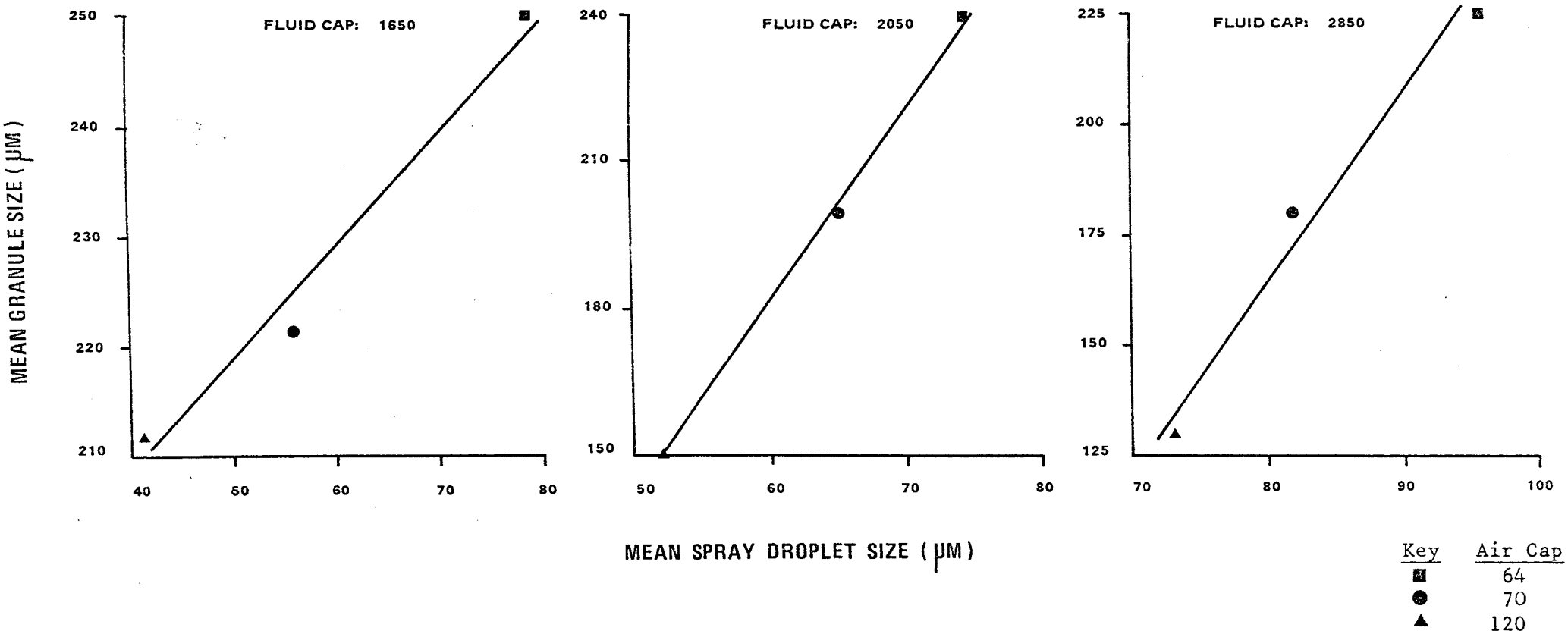


Fig. 4.9 Relationship between Spray Droplet Size and Final Granule Size produced in the Fluidised Bed

volume of granulating fluid compared to the small droplets and thus after collision with a particle(s) the combination unit will attain a high liquid bridge level. This results in a stronger association (high tensile strength) with the combination more resistant to the forces of disaggregation acting in the bed (i.e. attrition forces). Evaporation effects are also important. Sprays with a small droplet size evaporate more quickly due to the larger surface area generated. Results in Chapter 3 have shown that a coarser granule is produced when evaporation rates are low. The improved atomisation to produce smaller droplets does result in an increased droplet population, per unit volume of liquid, and therefore the probability of successful collision with powder particles(s) is increased. These combinations after collision may not however have sufficient liquid to become centres of optimum growth. This results in a slower growth rate with a narrower granule size distribution and smaller particle size being produced.

The relationship between spray droplet and granule size, which has been tentatively postulated in the past by several authors although never quantified due to spray characterisation difficulties, has been clearly demonstrated in this section of work. It is recommended that this area requires more detailed investigation since the ability to produce specific granule size distribution by relatively simple changes in spray atomisation has considerable potential. The benefits include improved weight uniformity, reduced granule batch to batch variation, improved granule compression characteristics and increased possibilities in solid dosage form design.

4.5.2 Effect of changing the process variables upon the spray characteristics

The results of the statistical analysis of the experiment of factorial design indicated that the factors investigated did exert an affect upon the Rosin-Rammler mean ($\bar{x}$), dispersion coefficient (w) and the spray rate of granulating solution. The results of this analysis are displayed in Table 4.6. It is perhaps easiest to discuss the significance of each variable individually upon the spray characteristics and finally, if possible, relate the spray droplet characteristics to the quality of granules produced within the fluidised bed.

4.5.2a Concentration of Granulating Solution

The concentration of granulating solution had no significant effect upon the Rosin-Rammler mean or the dispersion coefficient. This result is attributed to there being little difference between the viscosities of the two concentrations of solution investigated. Therefore similar amounts of energy are required to break up each solution into droplets. For solutions of high viscosity greater amounts of energy would be required for similar atomisation i.e. high atomising air pressures. A secondary factor would also come into prominence. This would be the effect of viscosity on the flow of liquid into the nozzle. However for pharmaceutical applications the liquids used in fluidised bed granulation are usually of low viscosities. This results in good atomisation and avoids the problem of nozzle blockage.

4.5.2b Spray Set-up

The type of spray nozzle used had a highly significant affect upon droplet size and distribution. This result was as expected since the nozzle sizes used greatly affected the rate of liquid addition. The data in Table 4.3. shows that the larger nozzle gave the largest $\bar{x}$ values. This is possibly due to the differences in flow rates through the nozzle since a higher air atomising pressure i.e. greater energy is required for the higher liquid flow rates. Thus at these high rates there is less efficient atomisation and this results in the large $\bar{x}$ value.

The distribution coefficient w was also affected with wider distributions obtained from the larger nozzle. This is again attributed to the difference in efficiency of atomising the various liquid flow rates together with the different design characteristics between the two nozzles.

4.5.2c Pressure

The influence of pressure upon spray characteristics has previously been demonstrated and discussed in section 4.5.1. The higher

the value of atomising air pressure applied to the system the greater the degree of liquid break-up i.e. atomisation. A further effect is that of widening the spray cone. This has great significance in Fluidised Bed Granulation since if the cone becomes too wide then the walls of the bowl become sprayed. This results in side wall aggregations and caking which can also affect fluidisation.

Also in this system the air pressure had a significant effect upon liquid flow rate. This is due to the results of the air pressure flowing through the nozzle exerting a siphon action which draws the granulating liquid into the nozzle chamber. Thus at high pressure there is greater siphon effect and thus increased spray rate, the combination of which ultimately affects the level of liquid atomisation.

4.5.2d Temperature of Granulating Solution

The temperature of the granulating solution has a significant effect upon $\bar{x}$ at the 97.5% level. The effects upon the spray are possibly due to a reduction in granulating solution viscosity at high temperatures, although with the system used this would be minimal as there is little difference in the viscosities of the liquids caused by a temperature change. Another explanation is the improved evaporation rates at higher temperatures thus immediately after atomisation there is liquid loss from the individual droplets. It is questionable whether this would apply to the results obtained using the Malvern Analyser since readings are taken instantaneously. This avoids inaccuracy inherent in other methods of spray droplet measurement as previously described. However it should also be noted that the atomising air exerts a cooling effect upon the granulating solution during atomisation.

Spray rate could also be affected since at high temperatures there is a reduction in liquid viscosity thus giving improved flow rates.

In conclusion of the four variables investigated it appears that the spray set up and the atomising air pressure have the most significant effect upon droplet size, distribution and spray rate.

4.5.3 Relationship between the Spray Characteristics and the quality of granulations produced from the 2^7 Factorial Design in Chapter 3

The effect of the four variables, temperature of granulating solution, concentration of granulating solution, atomising air pressure and nozzle design upon the characteristics of the generated spray have been discussed. It is not surprising that the spray characteristics are easily affected by these four variables. Several authors have investigated the effect of the spray granulating solution upon the physical properties of the granules produced within the fluidised bed. Up until now there has been great difficulty in,

a) Accurately measuring the spray characteristic of the atomised granulating solution.

b) Relating these results to the granules produced.

Schaefer and Wørts (1977 b) and Thurn (1970) are the only authors who have managed, to some degree to achieve this. Their method of droplet measurement used an oil droplet entrapment technique which does have inherent inaccuracies. Using the droplet data generated from the Malvern Analyser it is hoped to relate these characteristics to the physical properties of the granules prepared in Chapter 3. The three sets of data generated from the measurement of the characteristics of each spray were handled as follows. For each $\bar{x}$, w, or spray rate reading there are eight corresponding sets of granule data i.e. eight individual granule batches prepared using the same spray conditions. This is due to the factorial design of the experiment in Chapter 3, where seven individual variables were investigated. Three of these did not directly affect the atomisation of the spray thus were not used in the spray characterisation experiments. Thus these three remaining variables generate eight (2 x 2 x 2) individual granule batches prepared using identical spray conditions for each of the 16 different spray combinations investigated.

The spray characteristics i.e. droplet size, distribution and spray rate are listed in Appendix VI along with the rank order values (of granule quality as defined in Table 3.9) for each of the eight granule batches prepared from a specific spray combination.

The degree of association between the drop size ($\bar{x}$) data and the mean of the eight rank order values of overall granule quality was statistically assessed by calculating a correlation coefficient (see section 3.4.1). The above procedure was repeated for the results of the distribution (w) and spray rate values. Table 4.9 summarises the statistical analysis.

Table 4.9 Table of the degree of association of drop size ($\bar{x}$), distribution (w) and spray rate with mean overall rank order of granule quality.

	Drop Size ($\bar{x}$)	Distribution w	Spray Rate
Calculated Correlation Coefficient (r)	0.415	0.488	0.872
Level of Significance	90%	95%	99.9%

4.5.3a Drop Size ($\bar{x}$)

The analysis showed that there was indeed a relationship between granule quality and droplet size although only at the 90% significance level. The granule batch assessed as being of good pharmaceutical quality was manufactured from sprays with a large mean (Rosin-Rammler) droplet size. This confirms the findings of Schaefer and Wørts (1978a) and the theoretically based assumptions of Scott et al.(1964) Thus to obtain granules of a coarse nature a large mean droplet size is required.

4.5.3b Droplet Distribution (w)

As previously stated the Rosin-Rammler w is related to droplet size distribution. A high w value relates to a narrow size distribution. There is a strong relationship between w and granule quality. This is indicated by a positive correlation at the 95% significance level. The granule batches classified as being of good quality were obtained from the wider size distribution of the sprays generated. The probable explanation of this is that a wide size distribution gives different levels of localised wetting thus improving the probability of successful droplet/particle combinations that are able to form bonds of sufficient strength to prevent particle/particle deaggregation due to the attrition in the fluidised bed. The narrow droplet distribution of the sprays gave rise to the poorer granule batches. This can again be attributed to the lack of sufficient wetting with the theoretical combination of particle/droplet being limited to only two or three particles. Other factors which can be attributed to this are:

a) Quicker evaporation of the droplets.
b) Slower kinetics of granule growth resulting in the narrow uniform size distribution found with the poorer quality granules i.e. lack of granule growth over a large size range. The actual growth being limited to the smaller granules.

The manufacture of a granule with a narrow size distribution can however be advantageous. It can eliminate tablet weight uniformity problems and improve the dissolution profile of tablets.

4.5.3c Flow Rate

There is a highly significant effect of liquid flow rate through the nozzle upon the final quality of the granules produced. This result confirms the findings of the factorial experiment in Chapter 3. The larger spray rate i.e. the wetter the powders within the bed, the better the quality of the resulting granule batch. A similar result was achieved by Schaefer and Wørts (1978a).

It should be also noted at this stage that the effect of spray rate is of such magnitude that it may mask the significance of both the droplet size and distribution effect. Previous authors may have perhaps experienced this effect.

Further work is required in this field since a greater understanding of the spray system together with flow rate is the key to engineering a specific size distribution of granules. Thus granule batches of specified size distribution (from those of monosize to large aggregates) can be conveniently obtained by simple changes in the spray conditions.

4.6 OVERVIEW OF THE MALVERN ST 1800 DROPLET SPRAY ANALYSER

It is perhaps worth noting the advantages and disadvantages of the Malvern Droplet Analyser in the context of in situ measurement of droplet size distribution. The technique offers many advantages over the more traditional size measurement techniques and has great potential for use within the pharmaceutical industry in general. The technique has however received criticism in the use of the Rosin-Rammler distribution to fit the data. This criticism has been proved to be unfounded since it has been shown that the distribution is at the very least comparable to or better than existing distributions in describing a specific spray (Mugele and Evans, 1951). Later photographic work on drop sizing has shown good agreement with the Rosin-Rammler distribution for twin fluid atomisers (Frazer et al, 1963) and pressure swirl nozzles (Dombrowski and Tahir, 1977). The accuracy and limitation of this measurement technique was initially investigated by Azzopardi and Yeoman (1977). The instrument was tested with known particle size distributions and the results compared well with these. The sensitivity of the calculated energy distribution, to variations in the Rosin-Rammler parameters have also been examined (Negus and Azzopardi, 1978). It was found that the sensitivities claimed by Swithenbank et al (1976) were easily met. Problems can occur if the number of particles in the path of light is sufficiently high since multiple diffraction does occur and the light distribution reaching the detector is more spatially extended than given by the simple theory.

In general, time varying sprays do constitute a problem with the instrument although it is unaffected by the refractive index and transmission of the particles to be measured.

4.7 CONCLUSIONS

The investigation into the sprays produced by the atomisation of the granulating solution have shown that it can have a profound effect upon the quality of granules produced within the fluidised bed. The results derived from the experiment of factorial design show that the atomising air pressure and spray nozzle set up had a highly significant effect upon the Rosin-Rammler mean ($\bar{x}$), dispersion coefficient (w) and spray rate. The effect of these three parameters upon the quality of the granule produced was determined. Granule batches prepared in Chapter 3 and considered to be of good pharmaceutical quality were manufactured from sprays with a large mean droplet size ($\bar{x}$), wide size distribution (low w value) and high spray rate.

Further work using various types of spray nozzle is recommended since this will enable specific size distributions of granules to be manufactured. The pharmaceutical implications of this are obvious with the benefits of reduced variation in bioequivalence of granular products, improved tablet weight uniformity and reduced flow problems. In all a more uniformly controlled manufacture of a granule batch would result in improved tableting properties.

This work has also shown the importance of the droplet in the build up of granules during the spraying of granulating solution. It also highlights the need for a greater investigation into mechanism of growth within the bed and the effect of various process parameters (e.g. binding agent) upon this. The accurate droplet size measurement using the Malvern instrument has confirmed that the droplet/powder particle collisions require more attention.

CHAPTER 5

INFLUENCE OF POWDER MIX WETTABILITY UPON GRANULATION

5.1 INTRODUCTION AND SCOPE OF CHAPTER

5.2 THE EFFECT OF POWDER MIX HYDROPHOBICITY UPON FLUIDISED BED GRANULATION

5.2.1 Procedure for Granulation

5.2.2 Granule Testing

5.2.3 Results

5.3 MEASUREMENT OF WETTABILITY

5.3.1 Contact Angle Measurement

5.3.1.1 Direct Method

5.3.1.2 Indirect Methods

5.3.2 Determination of Contact Angle for Salicylic Acid/ Lactose Powder Mixes

5.3.2.1 Method

5.3.2.2 Determination of Liquid Properties

5.4 EFFECT OF SURFACTANTS ON POORLY WETTED POWDER MIXES

5.4.1 Procedure for Granulation

5.4.2 Granule Testing

5.4.3 Results

(i) Mean Particle Size

(ii) Flow Rate

5.5 TABLETING CHARACTERISTICS

5.5.1 Procedure for Tableting

5.5.2 Tablet Testing

5.5.3 Results

(a) Crushing Strength

(b) Tablet Density

(c) Tablet Weight Variation

(d) Dissolution Test

5.6 SPRAY DROPLET EVALUATION OF ATOMISED GRANULATING SOLUTIONS CONTAINING SURFACTANT

5.6.1 Determination of Spray Characteristics

(a) Smoked Paper Impingement Method

(b) Spray Droplet Analysis Technique

5.6.2 Results

5.6.2.1 Smoked Paper Impingement Records

(a) Assessment of spray droplet size distribution and pattern

(b) Assessment of spray cone width and break-up point

5.6.3 Discussion: The Influence of Spray Characteristics

(a) Increase in spray cone diameter

(b) Reduction in spray break-up distance

(c) Malvern results

5.6.4 Estimation of the number of SLS molecules per square metre of surface of each of the sprays

5.7 DISCUSSION

5.7.1 Reduced Spray Break-up Point

5.7.2 Increased Spray Cone Diameter

5.7.3 Reduced Mean Droplet Size

5.7.4 Sodium Lauryl Sulphate Molecule Concentration at the Air/Liquid Interface of the Atomised Spray

5.7.5 Relationship between the Method of Surfactant Addition to the Fluidised System and the Physical Properties of the Resulting Granules

5.7.6 Granule Properties

(a) Flow rates through orifice

(b) Particle size

5.7.7 Tablet Properties

(a) Crushing Strength

(b) Dissolution

5.8 CONCLUSION

CHAPTER 5

INFLUENCE OF POWDER MIX WETTABILITY UPON GRANULATION

5.1. Introduction and Scope of Chapter

The wetting of powders during the addition of granulating fluid to dry powders is an important factor in pharmaceutical granulation. In conventional wet granulation the shear obtained from various types of vertical shaft, sigma-bladed and horizontal shafted mixers assists this wetting. Where a more powerful kneading action is required, e.g. for hydrophobic materials, specifically designed mixers are available. The Diosna mixer gives an increased rate of shear which improves the wetting of hydrophobic powders with a resulting increase in granule strength.

In the process of fluidised bed granulation the ability of the droplets of granulating solution and powder particles to stick together governs the degree of granule build up. It was concluded from the results of the experiment of factorial design (Chapter 3) that the factors which produced a good quality granule were those which tended to increase the wetness of the granulation and delay its drying. If a hydrophobic component is added to the system then granulation becomes more difficult; the extra kneading action required to overcome this problem is absent. It is believed that many of the problems encountered by Industry have stemmed from this fundamental concept. Many pharmaceutical companies, having found that formulations were either too difficult or impossible to transfer to the fluidised bed granulator, have opted for high speed mixers.

Various workers (Wolf, 1968; Davies and Gloor, 1971 and 1972; Prioux et al, 1975; Crooks and Schade, 1978) who have investigated the process of fluidised bed granulation have mentioned that liquid penetration rates and wetting capabilities require more examination. Shinoda et al (1976) have shown that water soluble particles grow at a faster rate than water insoluble particles. Thurn (1970) concluded that if a powder mix showed a "hydrophobic excess" then aggregate disassociation occurred. The influence of starting materials was also examined by Schaefer and Wørts (1977a) using lactose/starch mixes. Their results showed that an increased starch content produced a

smaller final granule size. They concluded that no systematic investigation concerning the influence of the starting materials and their particle sizes on the growth of the final granules had been published and summarised by stating that further experiments using hydrophobic materials were necessary.

In order to quantify the effect of wettability upon granulation in this work, powder mixes of various degrees of hydrophobicity were studied. For this purpose combinations of salicylic acid and lactose were used. Salicylic acid was selected since it is extremely hydrophobic (θ = 103°), cheap, relatively non toxic and easily assayed. Lactose, on the other hand, is hydrophilic (θ = 30°). (Lerk et al, 1976)

This was followed by an investigation of the effect of surfactants on fluidised bed granulation. It was thought that the addition of the surfactant would reduce the interfacial tension between the granulating solution and the powder particles, increase wetting and therefore improve granulation. Surfactants have been shown in the literature to improve conventional wet granulation and subsequent tablet disintegration and dissolution (Cooper and Brecht, 1957; Beidebach, 1960; Kassein and Ghazy, 1974; Chodkowska-Granicka, 1968a, 1968b; Borzunov and Shevchenko, 1970).

A poorly wetted mix was then created by using a 50:50 blend of lactose and salicylic acid. Sodium lauryl sulphate was selected as the surfactant and added to the system in two ways: directly in the powder or dissolved in the granulating solution. Granulation was performed and the resulting granules were assessed and subsequently compressed. The physical properties of the tablets were then tested.

A droplet size distribution of the sprays containing surfactant was also measured and this information was used to explain differences in granule properties.

5.2. THE EFFECT OF POWDER MIX HYDROPHOBICITY UPON FLUIDISED BED GRANULATION

5.2.1. Procedure for Granulation

The optimised run conditions for each granulation were those shown in Table 4.7. The pressure spray system (as described in

section 2.2.1) was used at a liquid pressure of 1.4 bar to achieve a granulating solution addition rate of 200 ml in 10 minutes. Lactose and salicylic acid were mixed in the following proportions 100:0, 80:20, 60:40, 50:50, 40:60, 20:80, 0:100.

Prior to granulation the powders were presifted through a 1000 μm screen to break up any large agglomerates.

The basic procedure for each granulation was as follows: the salicylic acid/lactose charge was added to the product container after the inlet air temperature was stabilised. Prior to the addition of granulating solution the powders in the container were mixed by fluidisation for 30 s. The granulating solution was then sprayed onto the bed at the preset values. At the end of the spraying phase the supply of compressed air was terminated and both the fluidising air temperature and flow rate increased to 65°C and 30 x 10^{-3} $m^3 s^{-1}$ respectively. Each granulation was dried until a bowl temperature of 50°C was reached. This corresponds to a moisture content of approximately 2.0%

5.2.2. Granule Testing

A sieve analysis, as described in section 2.4.1, was performed on each batch of granules.

5.2.3. Results

The data generated from the sieve analysis of each granulation is displayed as histograms in Fig. 5.1. Increasing the hydrophobic content of the mix resulted in a smaller mean particle size and a narrower distribution with an increased peak height at the modal fraction. Fig. 5.2. shows that there is a linear decrease in mean particle size with increased salicylic acid component. In order to quantify hydrophobicity the degree of penetration and contact angle of each mix was measured.

5.3. Measurement of Wettability

The wetting of powders particularly in the pharmaceutical industry is an extremely important process. An indication of a powder's wettability is given by a contact angle measurement with a specific

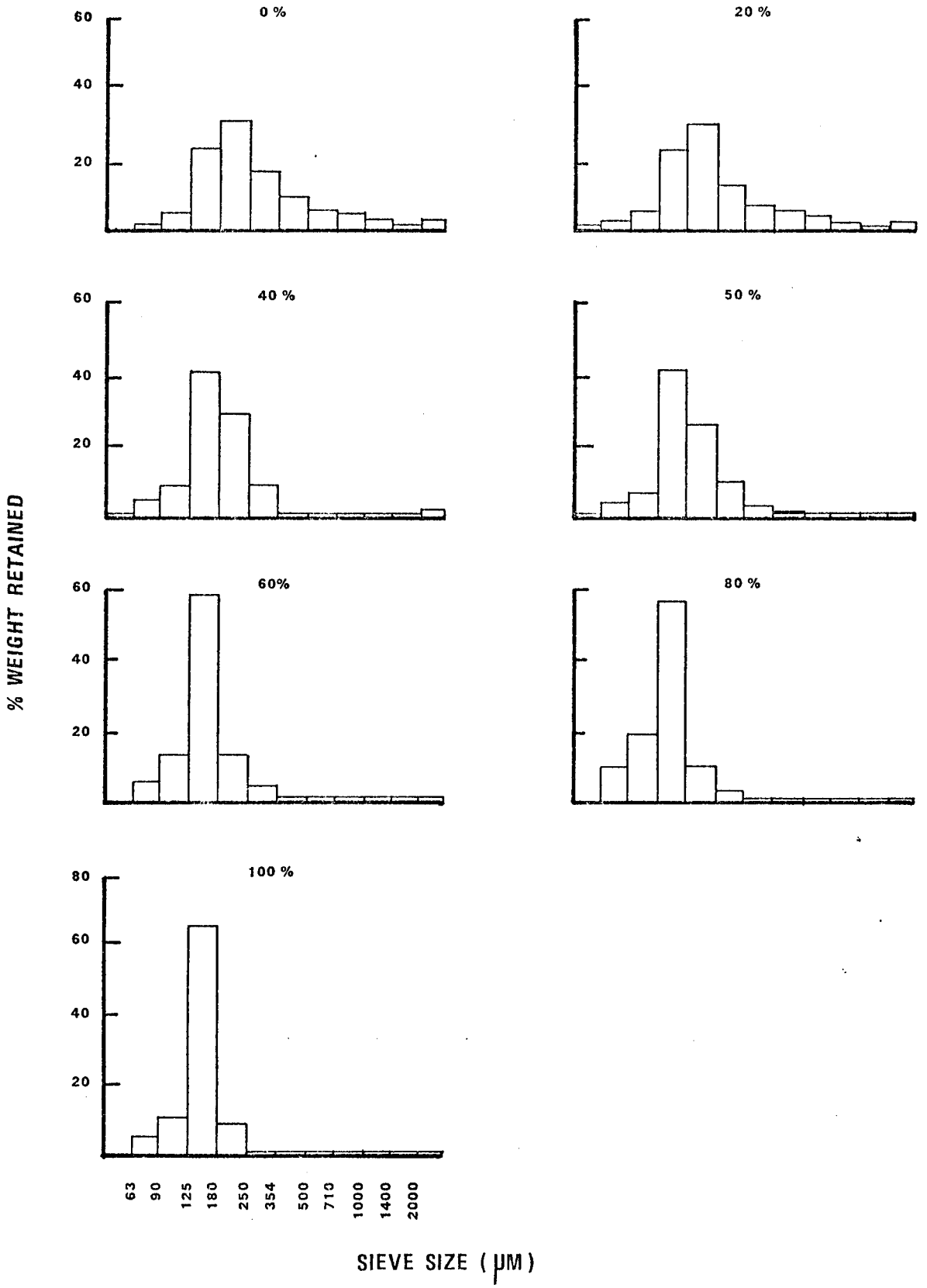


Fig. 5.1. Display of granule size distribution at a range of lactose/salicylic acid concentrations. The percentage quoted refers to salicylic acid content.

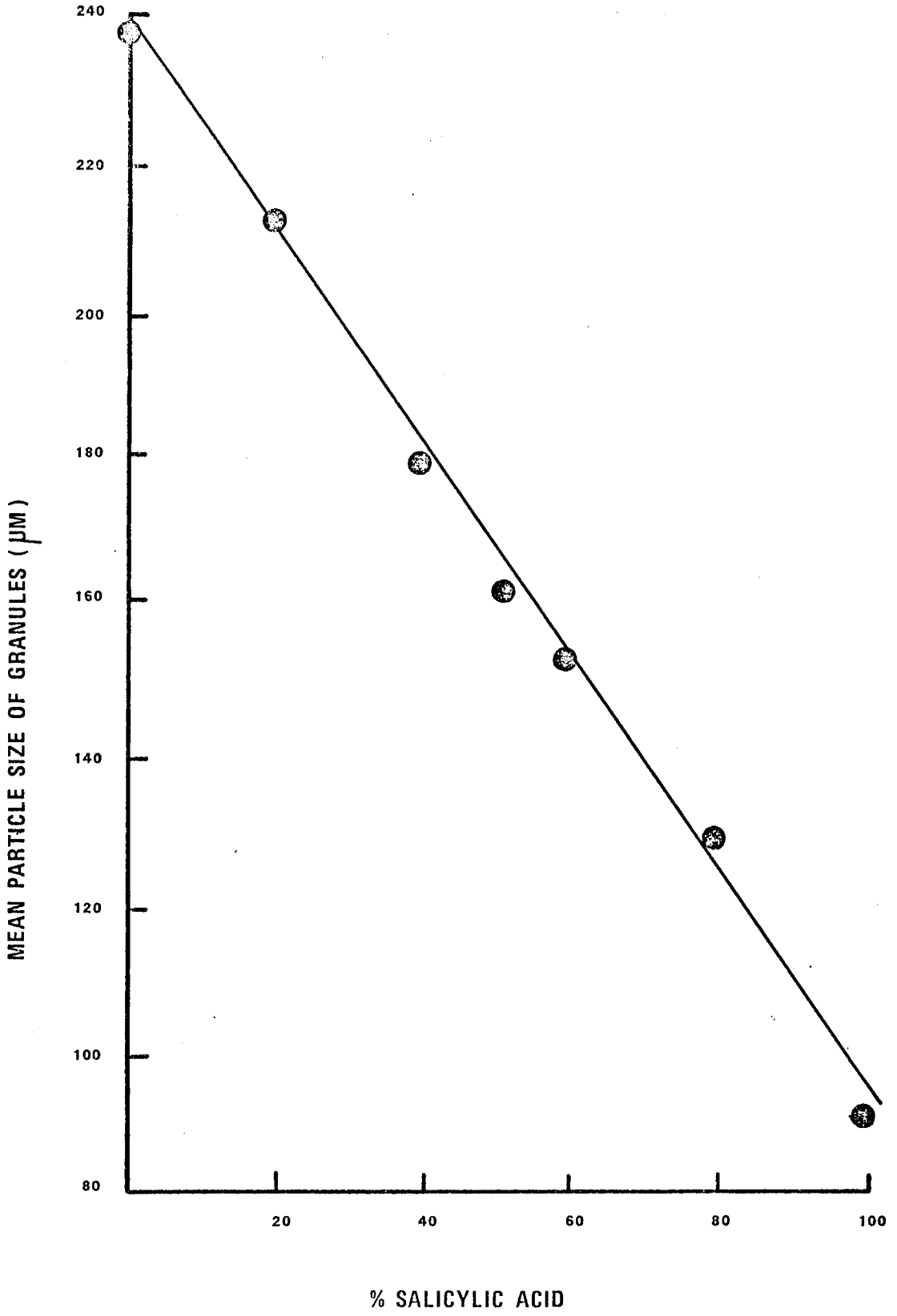


Fig. 5.2. Relationship between mean granule size and concentration of salicylic acid in the formulation.

liquid. This can be shown by considering the theoretical model suggested by Parfitt (1969) to distinguish between the three theoretical types of wetting namely: adhesion, immersion and spreading (Osterhof and Bartell, 1930).

When a drop of liquid is placed on a solid surface it may remain as a drop of finite area or it may spread indefinitely over the surface. The degree by which the droplet spreads is governed by the equilibrium between the interfacial energies associated with the liquid-solid interface (γ_{LS}), the gas-solid (γ_{GS}) and the gas-liquid (γ_{GL}) surfaces as shown by

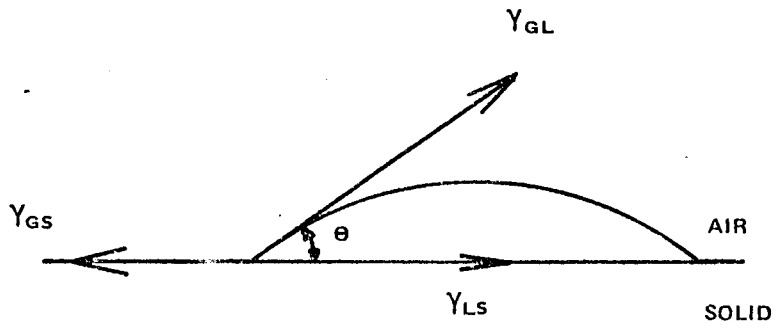
$$\gamma_{GS} = \gamma_{LS} + \gamma_{GL} \cos\theta \qquad \text{Eq. 5.1}$$

This equation is obtained by using the cosine rule to equate the opposing components of interfacial energy as indicated in Fig. 5.3 Equation 5.1 can be rewritten as

$$\cos\theta = \frac{\gamma_{GS} - \gamma_{LS}}{\gamma_{GL}} \qquad \text{Eq. 5.2}$$

thus the cosine of the contact angle gives the ratio of the energy gained in forming unit area of the solid-liquid interface to that required to form unit area of the liquid-air interface and thus is a measure of wettability (Cassie, 1948). A more detailed mathematical account of wettability using theoretical models to disinguish between types of wetting can be found in Johnson and Dettre (1966). Low values of contact angle indicates an easily wetted solid.

Fig. 5.3. Interfacial energy components for drop of liquid on a solid surface.



5.3.1 Contact Angle Measurement

The measurement of the contact angle of a powder is extremely difficult and it has been suggested that there is no precise method for determining it (Kossen and Heertjes, 1965). The methods available for estimating the angle can be divided into two groups.

5.3.1.1 Direct Method

This is a commonly used method which involves the direct measurement of a liquid drop resting on a plane solid surface. The contact angle is determined by constructing a tangent to the profile at the point of contact with the solid surface. This can be done on a projected image or photograph of the drop profile or, directly using a telescope fitted with a goniometer eyepiece. Advantages of the direct method are that it employs relatively simple instruments, it can be used on solids having a small surface area, and it requires only small amounts of liquid. Large errors do occur when trying to define the exact position of the liquid/solid contact point and is therefore preferably used by experienced operators.

5.3.1.2 Indirect Methods

Various methods are available to determine wettability expressed in terms of contact angle: such as the wetting volume, sedimentation, adsorption and heat of immersional wetting techniques. Two such methods have been extensively used to measure the contact angles of pharmaceutical materials. These are:-

(i) Penetration Method

Using the Washburn (1921) equation for the flow of a liquid through a capillary it is possible to calculate the magnitude of the advancing contact angle from the rate of penetration. Thus for a single capillary of radius, r, the length of flow, ℓ, in time, t, is given by,

$$\ell^2 = \frac{\gamma r t \cos \theta}{2\eta}$$

γ= surface tension of liquid

η= viscosity of liquid

A powder packed into a tube may be considered to consist of a bundle of capillaries of mean radius $\bar{r}$. By applying the Washburn equation to the system:-

$$\ell^2 = \frac{(C\bar{r})\ \gamma\ t \cos\theta}{2\eta}$$

where C is a constant to allow for randomly orientated capillaries.

This method has been used for contact angle determination of aqueous surfactant solutions on powders (Bruil and van Aartsen, 1974). Cook et al (1977) have also proposed its use in calculating the contact angles of hydrophobic drugs from penetration measurements employing mixtures of alcohol and water although they found that the angle was dependent upon the drug particle size. This has been shown by Carli and Simioni (1977 and 1979) to be due to a Washburn equation inadequacy since the quadratic relationship between length of penetration and time does not always hold. This was attributed to the type of pore distribution of the porous structure being penetrated.

(ii) Droplet Height Method

It has been shown (Padday, 1951), for a large drop of height, h, on a flat horizontal surface, that at equilibrium,

$$\cos\theta = \frac{1 - \rho_L g}{2\ \gamma_{LV^\circ}} \quad (h^2) \qquad \text{Eq. 5.3}$$

Kossen and Heertjes (1965), using the above equation corrected for surface porosity, have derived expressions for calculating the contact angle from the height of a liquid drop on a saturated powder compact. These are:

$$\text{for } \theta > 90^\circ \quad \cos\theta = -1 + \sqrt{\frac{(2 - \rho_L\ gh^2)}{2\gamma_{LV^\circ}} \frac{2}{3(1 - \varepsilon_V)}} \qquad \text{Eq. 5.4}$$

$$\text{for } \theta < 90^\circ \quad \cos\theta = 1 - \sqrt{\frac{2}{3(1 - \varepsilon_V)} \frac{\rho_L g\ h^2}{2\gamma_{LV^\circ}}} \qquad \text{Eq. 5.5}$$

where h is the height of the drop, ε_v is the volume porosity of the compact, ρ_L is the liquid density, γ_{LV} is the liquid surface tension and g is the acceleration due to gravity. In the derivation of these equations assumptions are made that allow the determination of surface porosity in terms of measurable volume porosity. The method has received criticism since it has been thought that the external physical properties of the powder may change under compaction and give anomalous results. Kossen and Heertjes (1965) however found comparable results between the contact angles obtained with a slab of sodium chloride crystal and with the compressed compact of powder. They indicated that small differences did occur but of negligible magnitude.

Lerk et al (1976) using a system of aspirin and dicalcium phosphate have shown that the above two equations can be used to measure the contact angles of two component powder mixes. A linear relationship between the cosine of the contact angle of the mixed system and the proportion of the components was obtained with small particle sizes. However with larger particle sizes the hydrophobic material dominated and did not obey the relationship of Cassie (1948) of a linear relationship between the cos θ of a heterogeneous surface and the area fraction of the components.

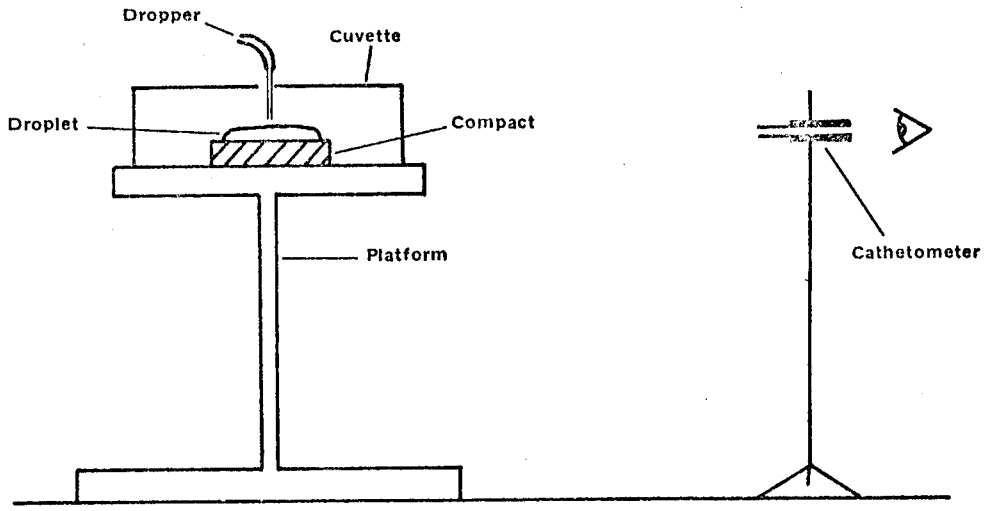
5.3.2 Determination of Contact Angle for Salicylic Acid/ Lactose Powder Mixes

The droplet height method of Kossen and Heertjes (1965) was used to measure the contact angle of the salicylic acid/lactose mixes. It has the advantages of only requiring simple measurements thus eliminating operator error and having already been shown to be applicable for a two component system (Lerk et al, 1976). Early attempts at using the simpler penetration method were unsuccessful due to the non-uniform penetration of the solvent front as it progressed up the powder bed. The droplet height method was thus adopted as the technique of choice.

5.3.2.1 Method

The apparatus is shown in Fig. 5.4 and consists of a cathetometer and an adjustable platform to ensure the horizontal position of the compact. The compact is surrounded by an inverted cuvette

Fig. 5.4. Apparatus for contact angle determination



with a hole in the bottom allowing passage of a narrow gauge syringe needle.

Each compact was identically prepared by premixing the powder(s) and distributing a nominal weight of 2.0g of mix in a 39.4mm diameter die. This was compressed at a rate of 0.4mm s^{-1} on a hydraulic press (Denison) until a pressure of 100 MPa was achieved. The compact was removed from the die, reweighed, the thickness measured and its porosity calculated.

The procedure for measuring droplet height was as described by Kossen and Heertjes (1965). This consisted of presaturating the powder compact with a solution of 5% $^{w}/v$ PVP saturated with lactose. The saturated solution was used to prevent compact dissolution. After saturation, the compact was placed on the horizontal platform and surrounded by the inverted cuvette. The lactose-saturated PVP solution was dropped slowly onto the compact surface from the needle and the readings of the drop height were taken with a cathetometer until additional drops caused no further increase in height. All measurements were carried out at room temperature (20°C) and in duplicate. The contact angle was then calculated from the appropriate equation (Eq. 5.4 and 5.5).

5.3.2.2 Determination of Liquid Properties

The surface tension of the lactose-saturated 5% PVP solution was measured by tensiometer (Du Nuoy) at 20°C see section 2.3.1. The density was measured using a specific density bottle also at 20°C (see section 2.3.2).

A list of measured values along with the calculated contact angle for each powder mix are given in Table 5.1.

A plot of the contact angle (cos θ) against percentage salicylic acid content in the powder mix gives a linear relationship (Fig. 5.5). This shows that as the amount of salicylic acid increases there is a corresponding reduction in the value of cos θ. A similar linear relationship is obtained when the mean particle size of each granulated powder mix is plotted against cos θ (Fig. 5.6). This indicates that a larger mean particle size is obtained from powder mixes with low contact angles (i.e. large values of cos θ). Thus a direct relationship has been found between mean particle size of granules and the wettability of powder.

It has therefore been shown that not only does wettability have a direct influence on fluidised bed granulation, but also that it manifests itself in a regular decrease in granule growth as the hydrophobicity of the powder mix increases. In order to overcome this wettability problem methods of improving powder mix wettability were subsequently investigated.

Table 5.1. Calculated Values of Contact Angle

% SALICYLIC ACID	COMPACT DENSITY ($g\ ml^{-1}$)	DENSITY OF POWDER MIX ($g\ ml^{-1}$)	POROSITY	SURFACE TENSION ($mN\ m^{-1}$)	DENSITY LIQUID ($g\ ml^{-1}$)	DROP HEIGHT (mm)	COS θ	θ
0	1.258	1.525	0.175	50.81	1.0673	0.37	0.8932	26.7
20	1.284	1.507	0.148	50.81	1.0673	0.88	0.7501	41.4
40	1.292	1.488	0.132	50.81	1.0673	1.67	0.530	58.0
50	1.286	1.479	0.130	50.81	1.0673	2.04	0.42679	64.8
60	1.282	1.470	0.128	50.81	1.0673	2.44	0.3152	71.6
80	1.281	1.451	0.117	50.81	1.0673	2.75	0.233	76.5
100	1.276	1.433	0.110	50.81	1.0675	3.09	-0.1298	92.9

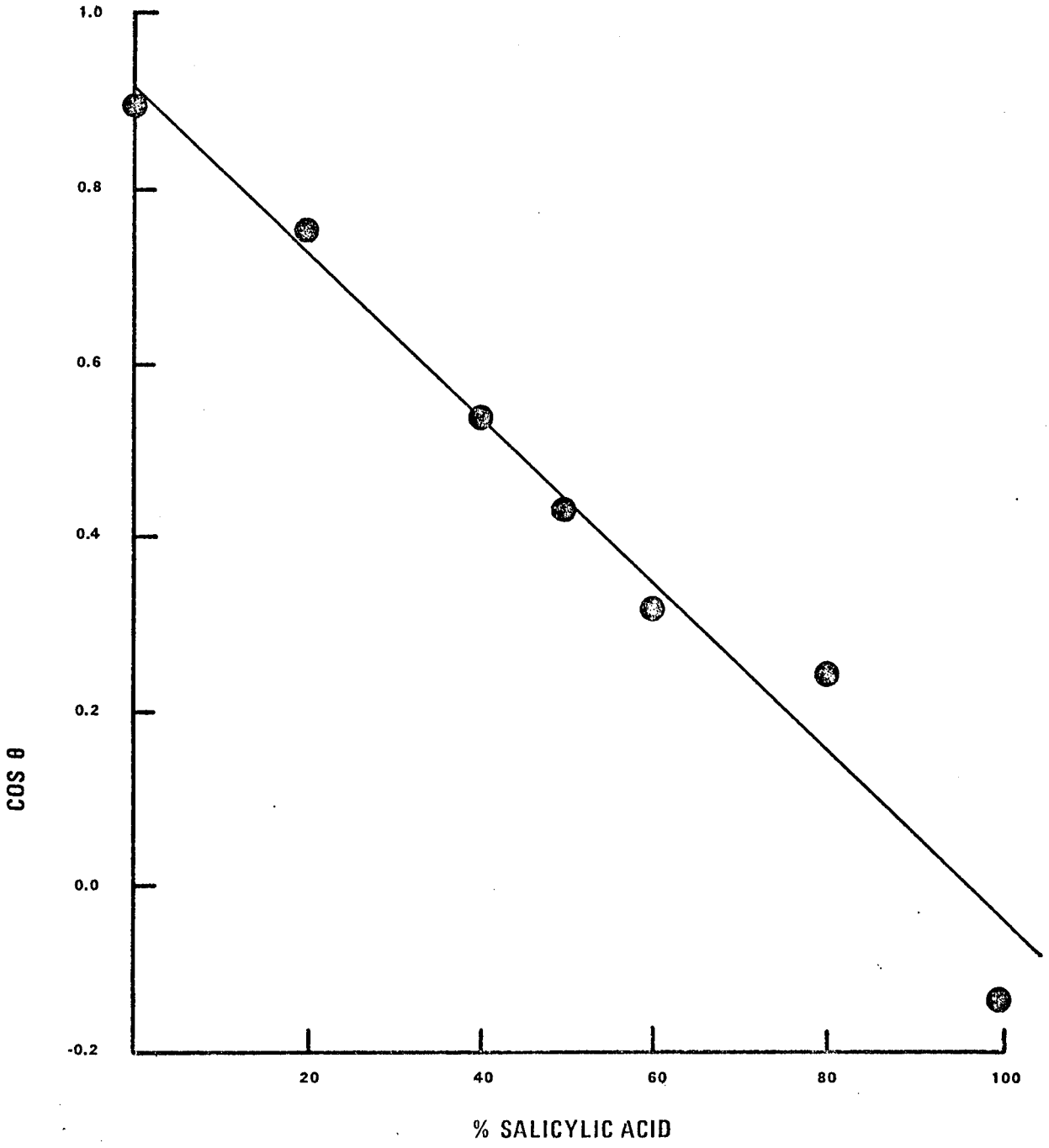


Fig. 5.5 Relationship between the cosine of the contact angle (cos θ) and the content of salicylic acid in the powder mix.

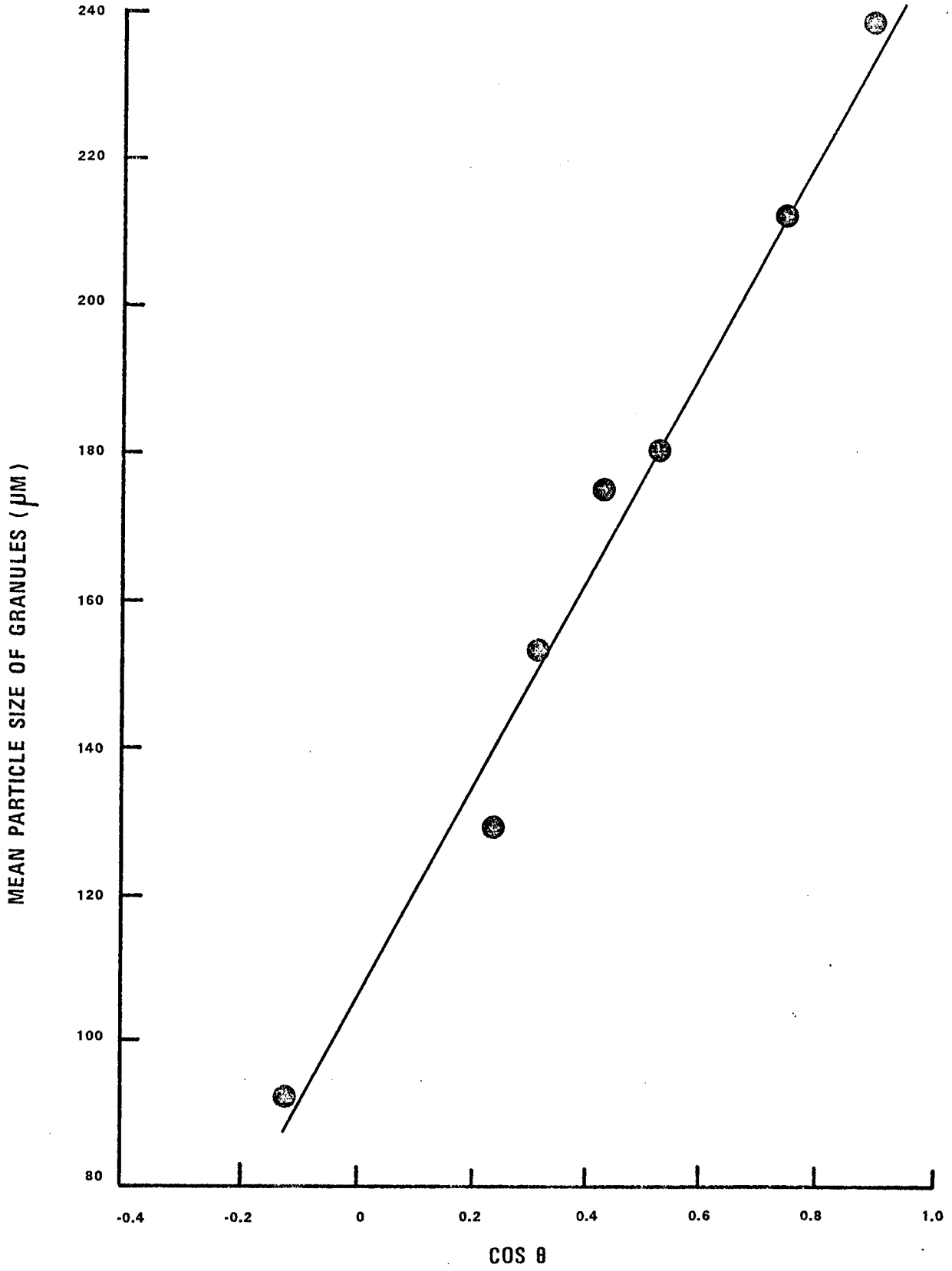


Fig. 5.6. Linear relationship between mean granule size against cosine of contact angle of the powder mix.

5.4. EFFECT OF SURFACTANTS ON POORLY WETTED POWDER MIXES

During granulation in the fluidised bed granulator the ability of the droplets of granulating solution to wet the powder particles governs the degree of granule formation. As previously demonstrated in section 5.3 if the hydrophobicity of the powder mix is increased there is a corresponding reduction in granule growth. This is due to the high interfacial tension between the hydrophobic particles and the droplet of granulating solution. It was thought that the introduction of a surface active agent to the fluidised system would help reduce the interfacial tension between the granulating solution and the powder mix particles, increase wetting and thus improve granulation.

The use of surface active agents in conventional wet granulation is not uncommon and several reports of their incorporation into tablet formulation can be found. Ward and Trachtenberg (1962) have reported reduced granulating times while Cooper and Brecht (1957) have advocated their use as disintegrating agents. Improved drug dissolution has also been shown (e.g. Levy and Gumtow, 1963).

Sodium lauryl sulphate (SLS) was selected as the model surfactant and added to the FBG system in two ways:-

(i) to the powder mix
(ii) dissolved in the granulating solution.

In the powder mix SLS was added in concentrations of 0.5, 1, 2.5, 5 and 7.5% $^{w}/_{w}$ of the powder charge. The concentrations used in the granulating solution were also 0.5 to 7.5%, but werecalculated as % $^{w}/_{v}$ of the granulating solution. These concentrations were selected to investigate whether there was a similar localised effect to that when the SLS was added to the powder since in each case their respective concentrations in the particle/droplet/particle combination would be the same. The actual overall concentration of SLS in the final granule however ranged from 0.13 to 1.9% $^{w}/_{w}$.

A 50:50 powder mix of salicylic acid and lactose was used to create a poorly wetted system.

5.4.1. Procedure for Granulation

Each granulation was manufactured as described in section 5.2.1 with the optimised run conditions remaining unchanged. When added to the powder mix, the SLS was premixed with the salicylic acid. With the surfactant in the granulating solution, the SLS was dissolved in water along with the required quantity of PVP.

5.4.2. Granule Testing

A sieve analysis and flow through a 9.5mm orifice was carried out on each batch of granules as described in section 2.4.

5.4.3. Results

(i) Mean Particle Size

The effect of the addition of sodium lauryl sulphate on the mean particle size of the final granulate is shown in Fig. 5.7. In general there is a linear increase in size with increased concentration of SLS. A greater rate of increase is exhibited by batches with SLS initially in the powder mix. In fact a doubling in mean granule size (160 to 310 μm), as compared with no SLS, is achieved with a 7.5% concentration. A similar but less marked increased is reflected in the granules prepared with the SLS added via the granulating solution; a maximum particle size of only 213 μm is achieved with the corresponding 7.5% $^{w}/_{v}$ concentration. If, however this concentration is corrected to the true overall amount of SLS in the final granule formulation then a slightly better increase is observed.

(ii) Flow Rate

The effect of sodium lauryl sulphate upon rate of discharge through a 9.5 mm orifice is displayed in Fig. 5.8. The overall result of adding SLS is an increase in the flow rate through the orifice. This increase however becomes less marked at concentrations in excess of 2.5%. The granulations with SLS in the powder mix give similar but slightly higher flow rates than the batches with SLS added via the granulating fluid even though their average particle sizes are quite different. When the flow rates of the granulations prepared by adding the surfactant via the granulating solution are replotted to give the overall concentration in the final granulation a greatly improved flow rate profile is obtained.

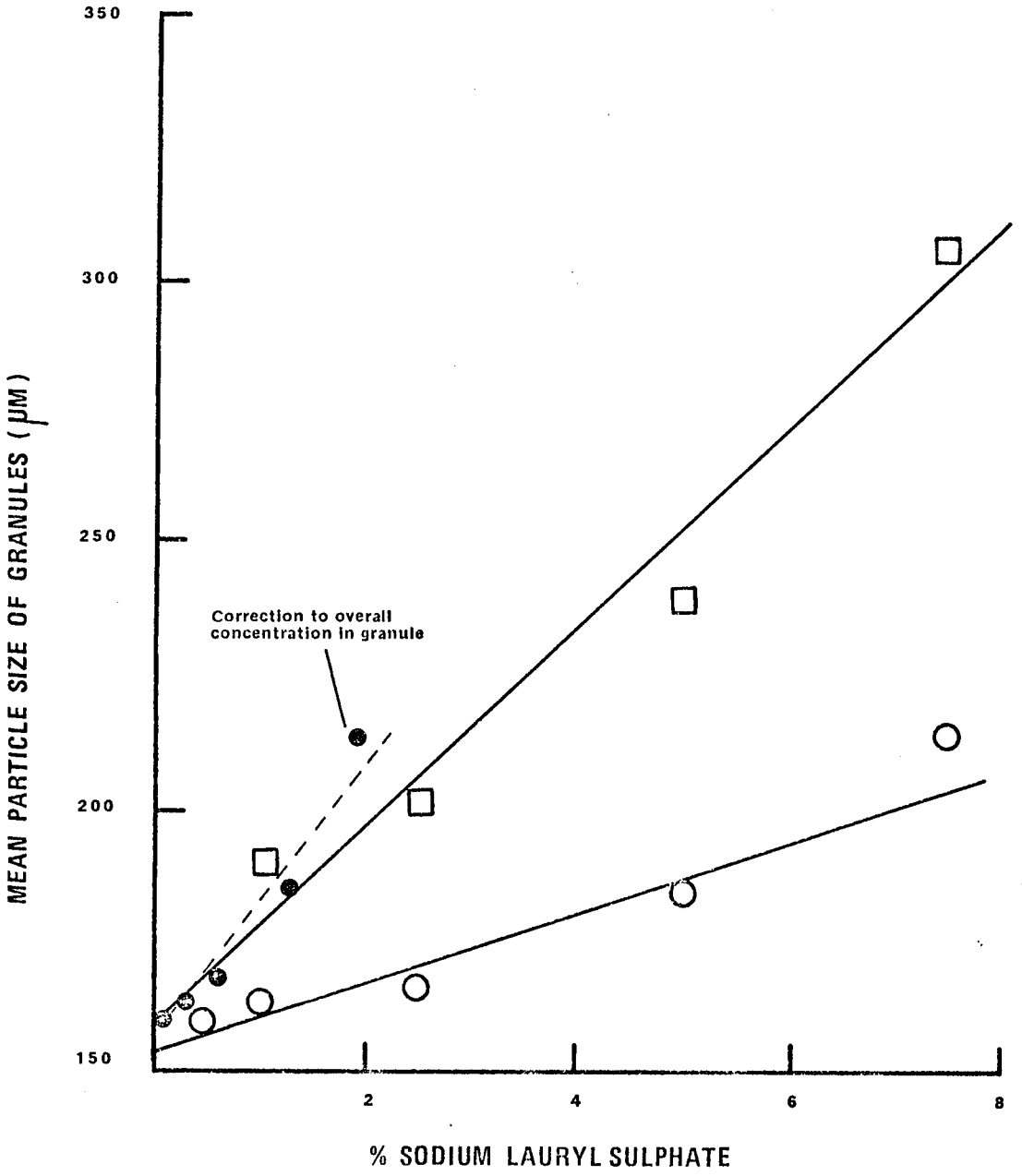


Fig. 5.7 Effect of sodium lauryl sulphate added directly to powder mix (□) or dissolved in the granulating solution (○) upon mean particle size of the resulting granulation. ((●) correction to overall concentration in granule.)

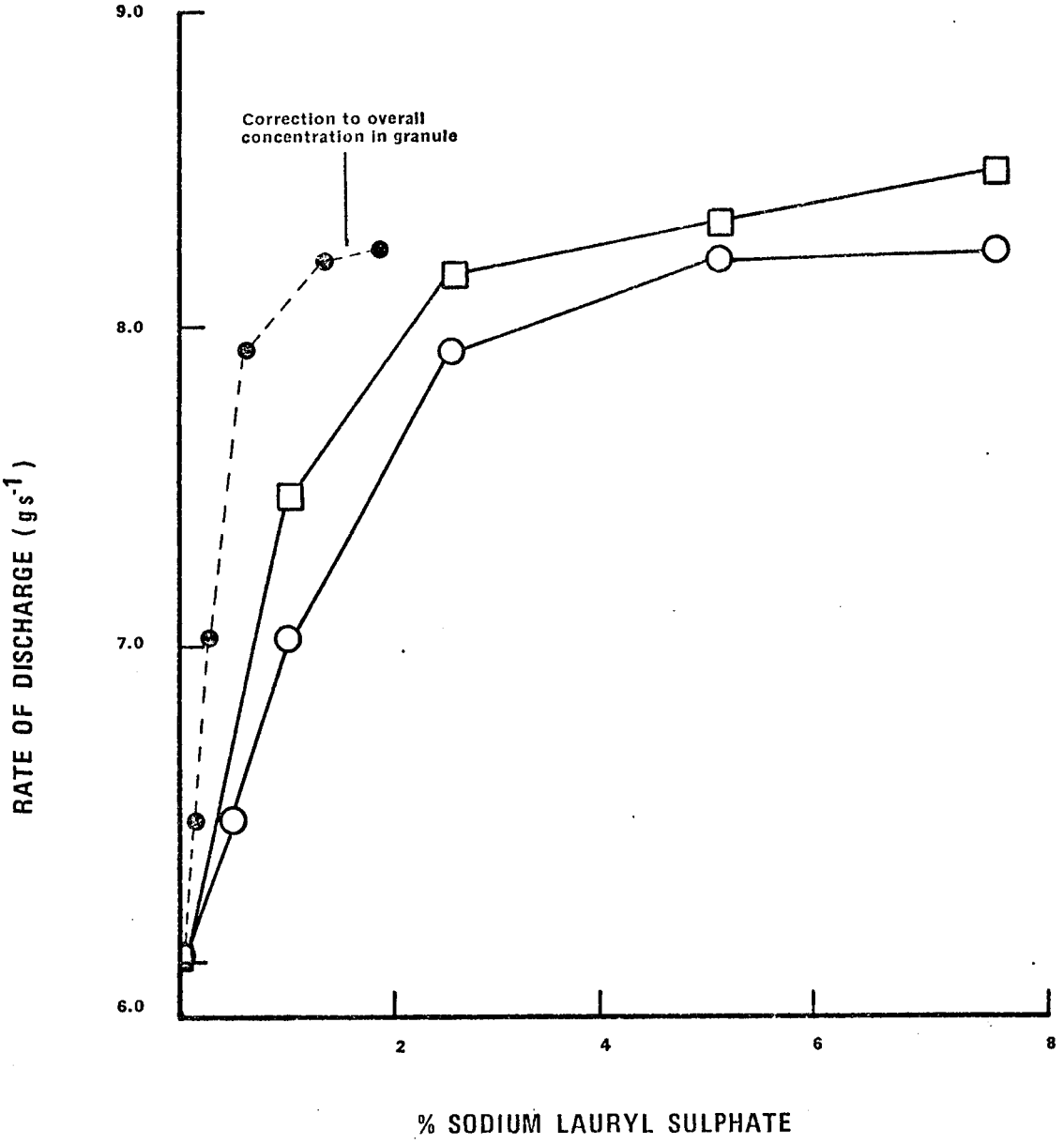


Fig. 5.8 Effect of sodium lauryl sulphate added directly to the powder (□) or dissolved in the granulating solution (○) upon rate of discharge of the resulting granules through a 9.5 mm orifice. ((●) correction to overall concentration in granule)

The results of mean particle size and flow rate for the granulations containing surfactant thus indicate that a slightly better improvement is obtained when the surfactant is added to the system dissolved in the granulating solution.

5.5. TABLETING CHARACTERISTICS

5.5.1 Procedure for Tableting

To complete the investigation into the effects of adding surfactant to the powder mass during fluid bed granulation the compression properties of each batch of tablets were assessed. Prior to compression each granule batch was passed through a 1.4mm screen to remove any overgranulated material which would otherwise have caused hopper blockage. Tablets of 12.5 mm diameter, nominally 625 mg were then prepared at a range of compaction forces up to 160 MPa using an instrumented Manesty BB3B tablet machine (see section 2.6). The single punch used was of shallow curvature and the machine speed was 32 rpm. Magnesium stearate was not added to the granule blend since surfactants have previously been used as lubricants (Wolff et al, 1947).

5.5.2 Tablet Testing

The physical properties of each set of tablets produced were assessed using the routine tests as described in section 2.7. These tests being:

(a) crushing strength (10 replicates)
(b) thickness (10 replicates)
(c) weight variation (10 replicates)
(d) tablets compressed, at 120 MPa compaction pressure from each granule batch, were further subjected to a dissolution test. This consisted of using a rotating basket method in simulated gastric juice (see section 2.7.6). The total salicylic acid dissolved in the dissolution medium was determined for each sample and these values expressed as percentages of the total salicylic acid content of the tablet under test.

5.5.3 Results

(a) Crushing Strength

The relationships between the diametral crushing strength and compaction pressure for tablets prepared from each batch of granules are shown in Fig. 5.9. For tablets containing no surfactant a characteristic peaked curve was obtained reaching a maximum at (160 MPa) after which tablet lamination occurred. The effect of adding SLS to the powder mix upon the compaction force crushing strength profile is shown in Fig. 5.9a. There is a general reduction in crushing strength as the amount of SLS is increased. At concentrations between 2.5 - 7.5% there is a plateauing effect at 5 - 6 kg crushing strength. A similar effect was obtained with the surfactant dissolved in the granulating solution (Fig. 5.9b). Again there was a reduction in crushing strength with increased SLS together with a plateauing between 2.5 - 7.5% at 5 to 6 kg crushing strength.

A further graph was plotted (Fig. 5.10) at a constant compaction force of 120 MPa to highlight the effect of surfactant concentration upon crushing strength. Small amounts of SLS have a marked effect upon strength although at concentrations above 2.5% there is little effect. Both sets of results give similar curves , but if the concentration of surfactant in the granulating solution is converted to overall concentration there is a more marked reduction in crushing strength than had previously been demonstrated.

(b) Tablet Density

Tablet density was calculated from tablet weight and thickness for each batch of tablets compressed. No significant differences between the compressed batches of granules were observed.

(c) Tablet Weight Variation

From the individual weighings of twenty tablets from each batch of granules a coefficient of variation was calculated and plotted against compaction pressure. No differences were observed; this was probably due to each granulation's excellent flow properties as previously demonstrated in Fig. 5.8.

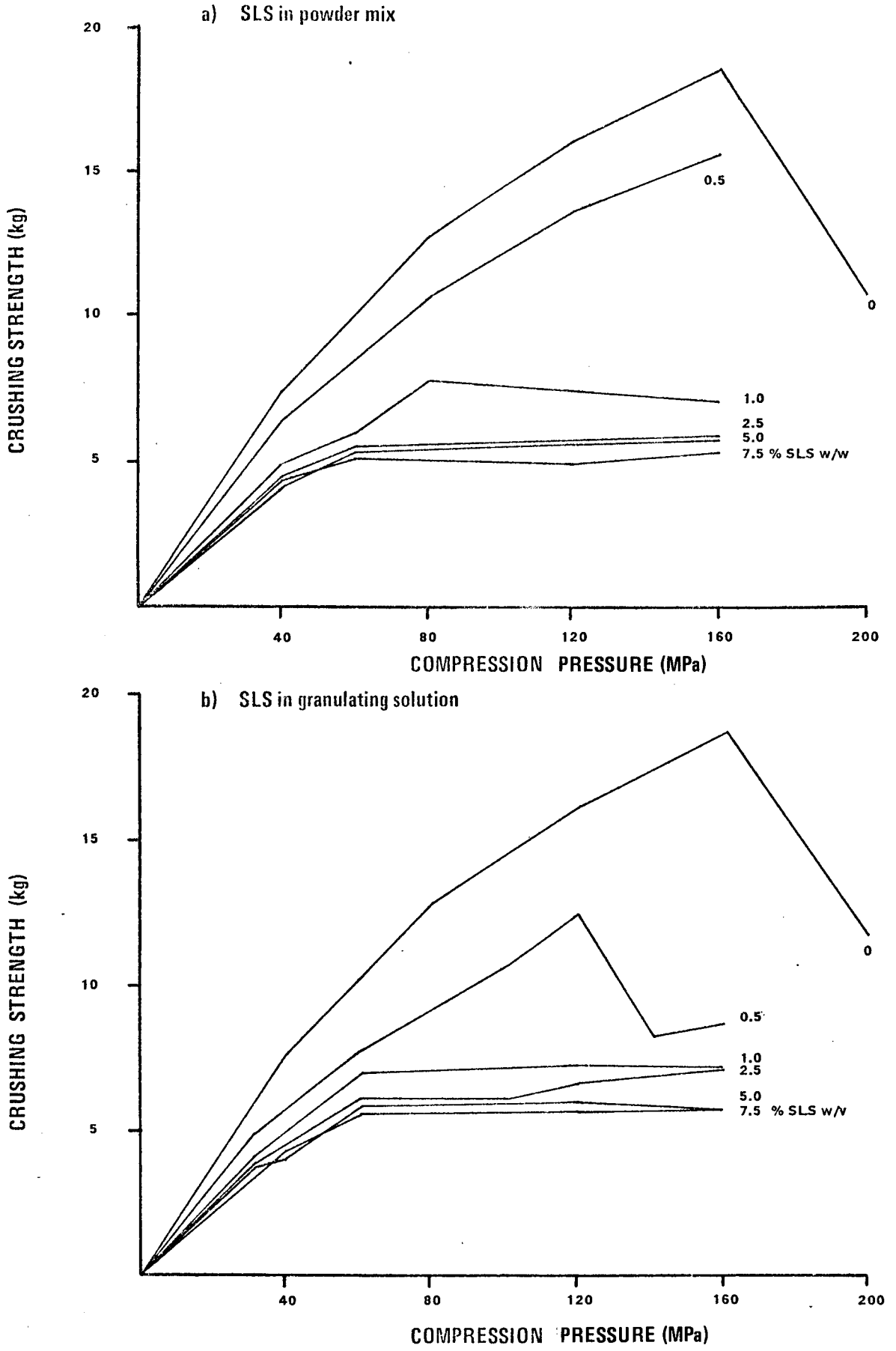


Fig. 5.9. Crushing strength - compression pressure profile for tablets containing sodium lauryl sulphate.

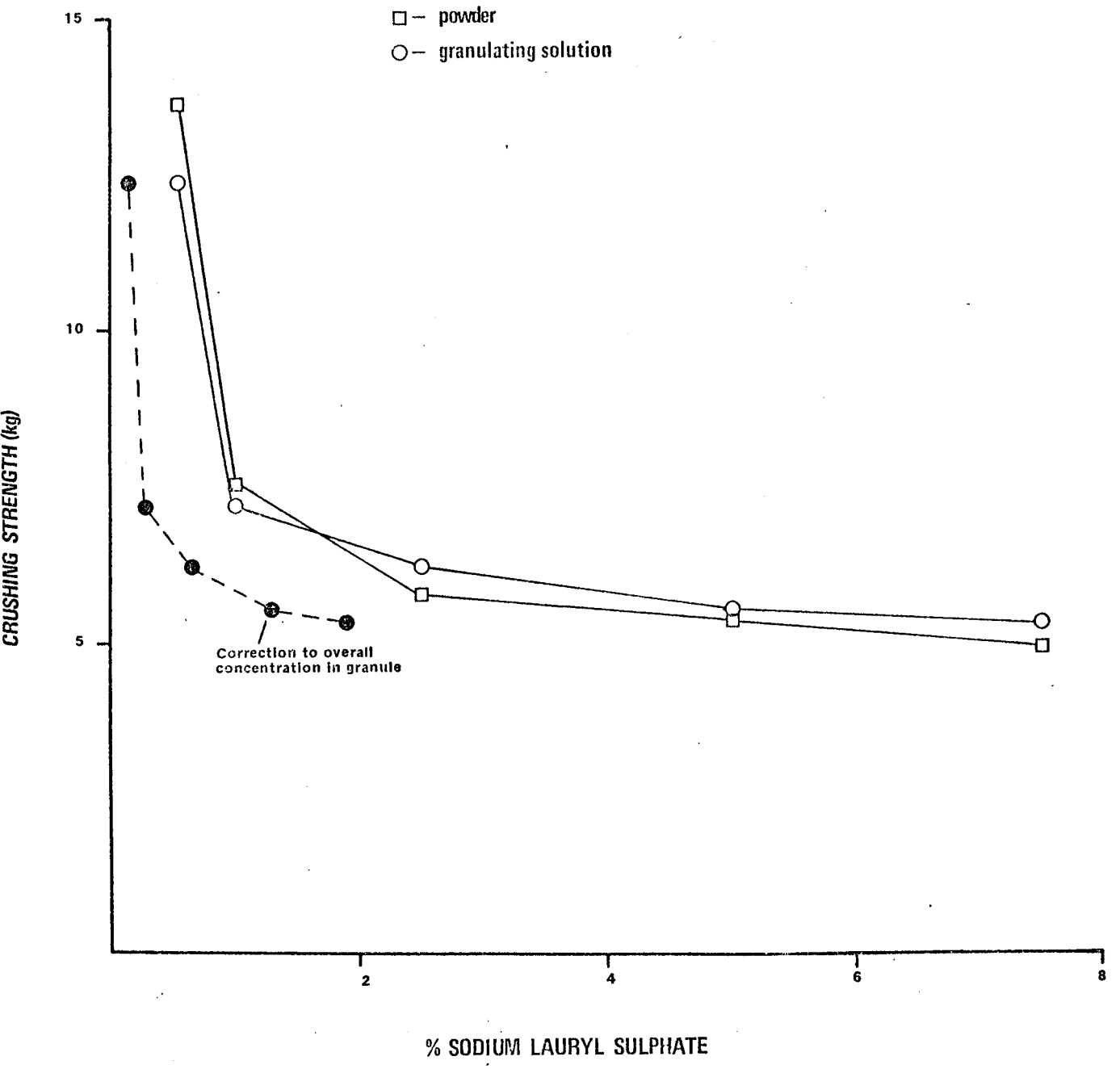


Fig. 5.10. Effect of concentration of sodium lauryl sulphate upon crushing strength at 120 MPa compaction pressure

(d) Dissolution Test

The effects of adding SLS in the powder mix or dissolved in the granulating solution on release of salicylic acid from each batch of tablets compressed at 120 MPa are shown in Figs. 5.11 and 5.12. The rate of release of tablets containing no surfactant was slow with approximately 50% salicylic acid being released in three hours. The dissolution profiles for tablets prepared with surfactant added to the powder mix are shown in Fig. 5.11. As the concentration of SLS is increased there is a corresponding increase in the release rate of salicylic acid. This increase is similar but less pronounced with tablets prepared with surfactant added dissolved in the granulating solution (Fig. 5.12).

A further graph was plotted of $t_{30\%}$ against concentration of surfactant for both series of tablet batches (Fig. 5.13). This highlighted the difference in release rates as indicated in Figs. 5.11 and 5.12. However, if the concentration of surfactant dissolved in the granulating solution is converted to overall concentration then the points are similar to the data generated from surfactant dissolved in the powder mix. This indicates that the rate of salicylic acid release is related only to the overall concentration of SLS present, there being no additional effects resulting from the method of addition of the surfactant to the formulation.

5.6 SPRAY DROPLET EVALUATION OF ATOMISED GRANULATING SOLUTIONS CONTAINING SURFACTANT

It was considered that the influence that the surfactant has upon the granulating solution spray may partially explain the differences in physical properties found between the two sets of granules.

The effect of the sodium lauryl sulphate dissolved in the granulating solution upon the spray pattern was assessed initially by the smoked paper impingement method. Although this method has limitations it does give a qualitative comparison between the sprays, and any major differences resulting from the presence of dissolved surfactants. Additionally the smoked paper impingement records enabled measurements of the droplet spray width to be noted. Observable

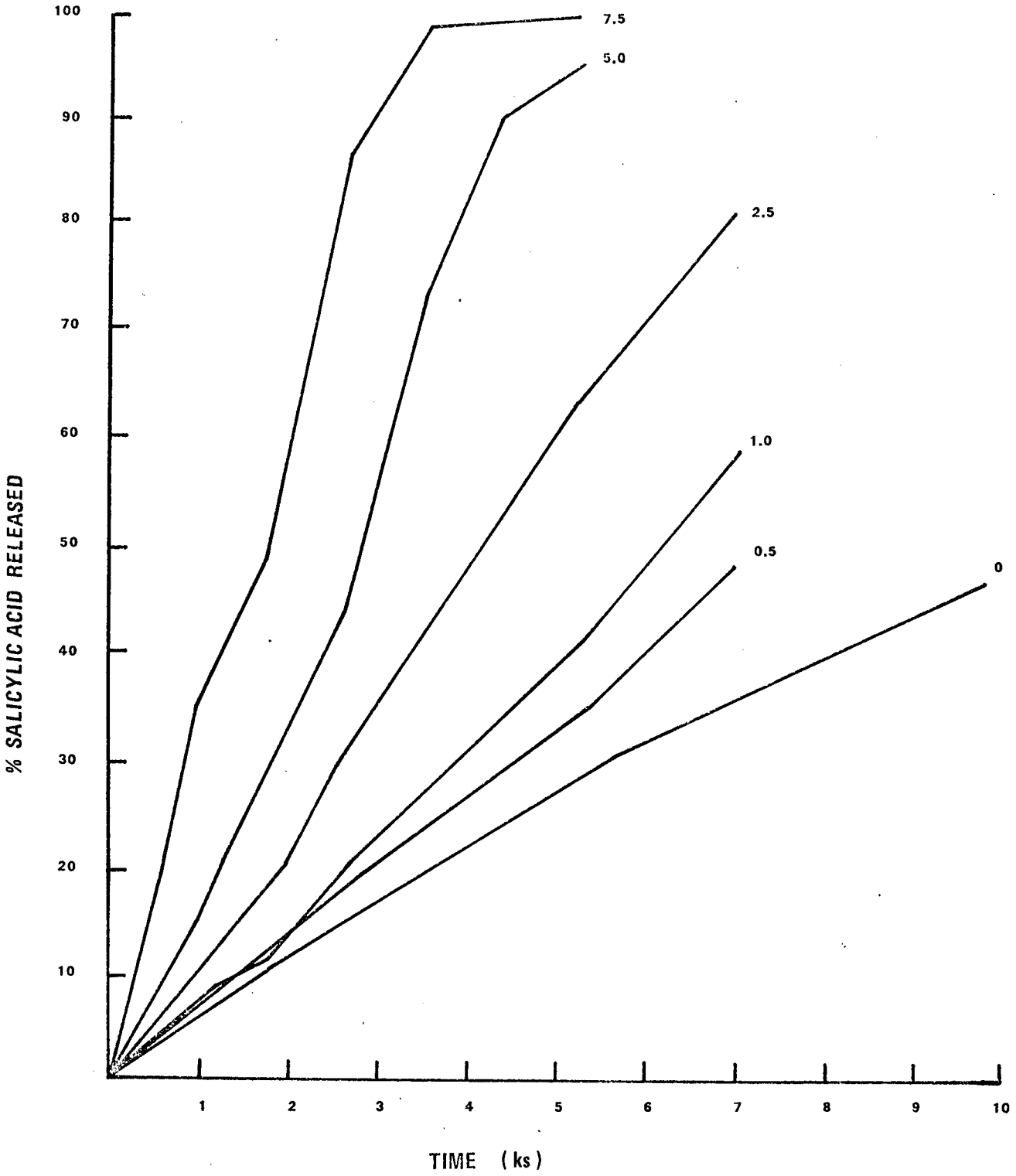


Fig. 5.11. Graph of percentage salicylic acid released against time for tablets prepared with sodium lauryl sulphate (SLS) added directly to the powder.
(Numbers on curve represent % $^{w}/_{w}$ SLS in powder)

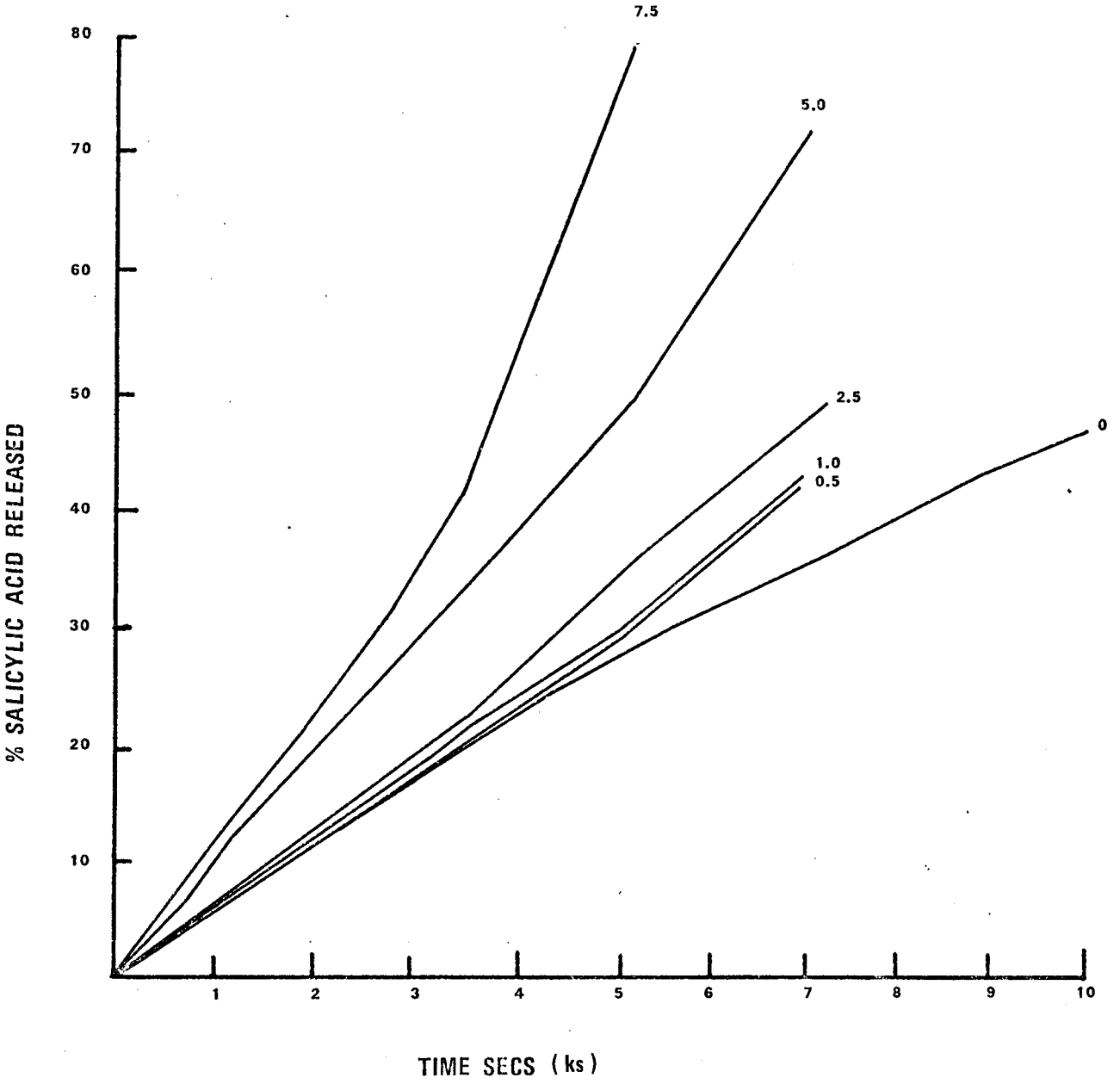


Fig. 5.12. Graph of percentage salicylic acid released against time for tablets prepared with sodium lauryl sulphate(SLS) added dissolved in the granulating solution.
(Numbers on curve represent % $^{w}/v$ SLS in granulating solution)

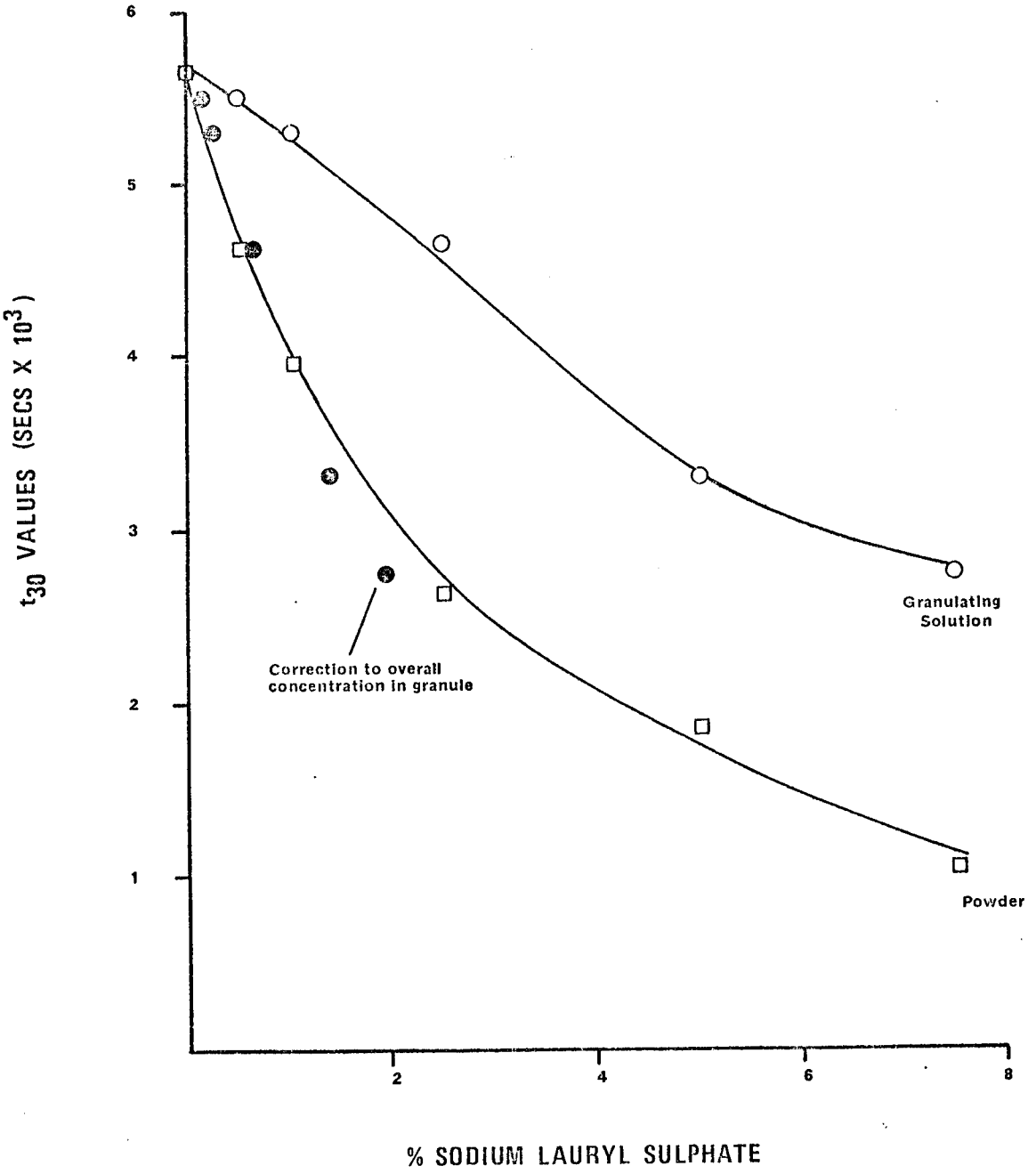


Fig. 5.13. Effect of sodium lauryl sulphate concentration on t_{30} values of tablet dissolution.

differences in the spray pattern were noted; thus each SLS containing spray was quantified by a droplet size analysis performed using the Malvern Droplet Spray Analyser.

The differences in rate of flow and mean particle size of the granules found in Figs. 5.7 and 5.8 as a result of the different mode of addition of SLS were considered to be due to the effect that the surfactant had upon the atomisation of the granulating solution. This effect was considered to manifest itself in an increase in spray droplet population with increased surfactant concentration together with a reduction in surface tension resulting in an improved spray atomisation. Also when the SLS is present in the spray it is more readily available in that it does not have to dissolve before exerting an effect.

The results of the spray measurements were further used to calculate the area generated by each spray for a fixed volume of liquid. This enabled the distribution of surfactant within each drop to be calculated and compared with the theoretically calculated area for distribution at the critical micelle concentration.

5.6.1 Determination of Spray Characteristics

(a) Smoked paper Impingement Method

The method has previously been described in section 4.2.2b. Additional spray records were taken at various distances from the spray nozzle to determine spray cone dimensions.

Each series of smoked drum records produced at distances of between 100 to 350 mm from the nozzle was measured for each concentration of SLS in the granulating solution.

(b) Spray Droplet Analysis Technique

A droplet size analysis of each spray was determined with the Malvern Droplet Spray Analyser using the method previously described in section 4.2.3.

5.6.2 Results

5.6.2.1 Smoked Paper Impingement Records

(a) Assessment of spray droplet size distribution and pattern

The smoked drum records are reproduced in Fig. 5.14. As the concentration of SLS dissolved in the granulating solution was increased there was an increase in the number of droplets recorded on the smoked paper. (although this is not clear in photographic reproduction) Further evaluation of these spray records of a more quantitative nature was not possible. However the records indicate the need for a more quantitative examination of the individual sprays.

(b) Assessment of spray cone width and break-up point

The diameter of the cone reproduced on each smoked record is displayed diagrammatically in Fig. 5.15. As the concentration of SLS increases there is a two-fold effect upon the dimensions of the spray cone. These are an increase in cone diameter with increased concentration and a reduction in spray break up distance.

5.6.3 Discussion: The Influence of Spray Characteristics

(a) Increase in spray cone diameter

This is possibly due to the increased concentration of SLS reducing the surface tension of the granulating solution thus improving the atomisation. The net result is that less energy is required for this break up and a wider spray diameter is obtained. This can be advantageous since it enables the spray cone diameter to be adjusted without using any mechanical means. The wider spray diameter has also the advantage of giving an increased spray to bed contact area thereby enhancing the possibility of droplet/particle collision. As shown in Fig. 5.15 the diameter of the cone 200mm from the nozzle increases from 65mm to 110mm as the concentration of SLS increases from 0% to 7.5%. This effectively increases the area of spray/bed contact from $3.3 \times 10^3 mm^2$ to $9.5 \times 10^3 mm^2$; a three fold increase in contact area. This increase in the number of droplet/particle collisions also correlated with an increase in mean particle size of the granules produced within the fluidised bed.

Fig. 5.14. Enlarged photographs of smoked drum impingement records of sprays containing sodium lauryl sulphate. (magnification x3)

Key	% SLS
O	0
◒	0.5
◑	2.5
◐	5.0
●	7.5

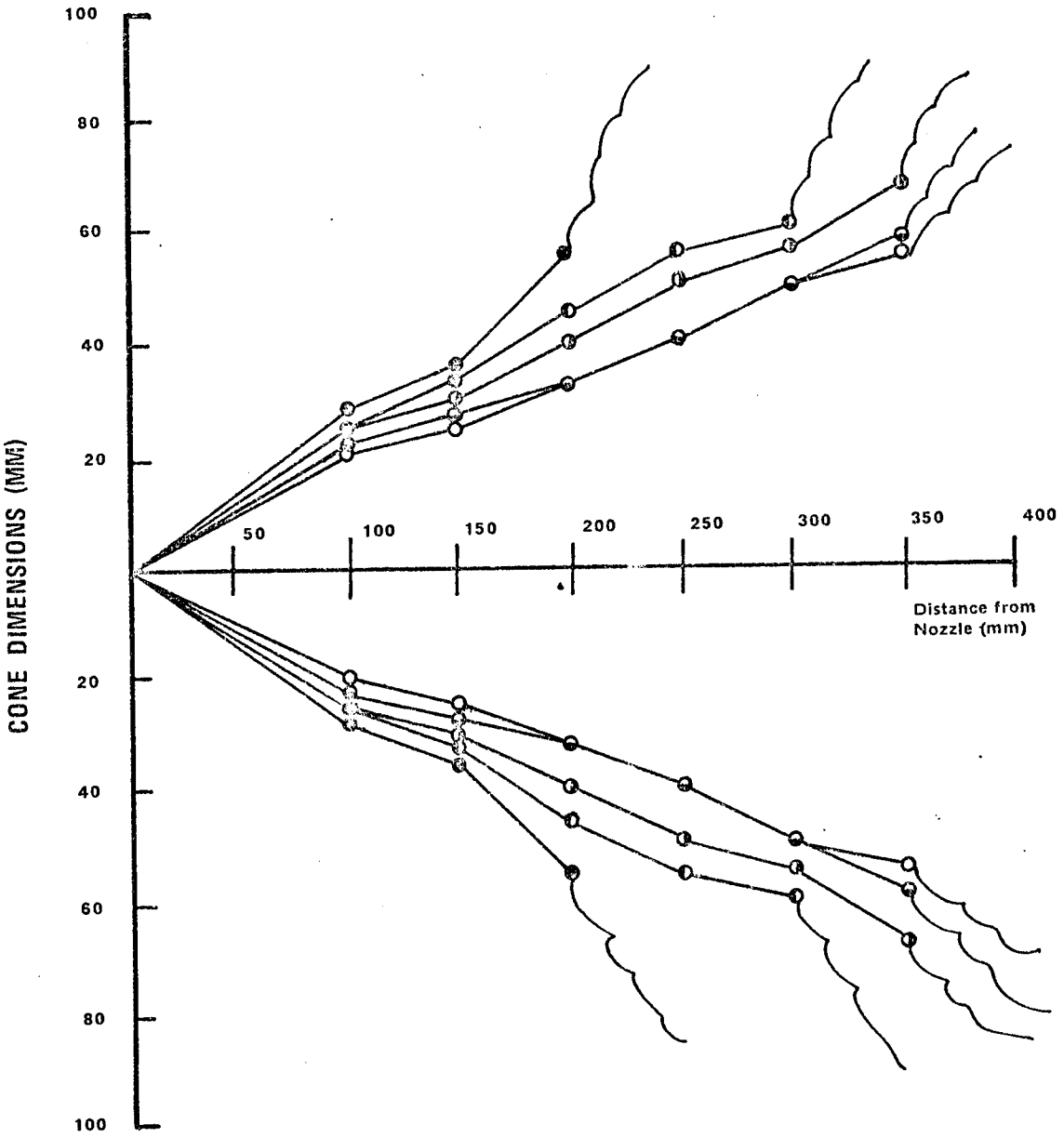


Fig. 5.15. Diagrammatic representation of the effect of sodium lauryl sulphate upon spray cone diameter and break up distance.

(b) Reduction in spray break-up distance

The break up point is defined as the distance up to which a spray maintains its general shape and pattern. After this distance the projected spray becomes turbulent. As the concentration of surfactant in the granulating solution increases there is a corresponding decrease in this break up distance. For a concentration of 7.5% surfactant this distance is 200mm which coincidentally corresponds to the same distance within this fluidised bed granulator between the nozzle and the surface of the fluidised bed of powders. For concentrations of 0, 0.5, and 2.5% the distance is approximately 350mm whilst for a solution containing 5% surfactant an intermediate distance of 300mm is obtained.

(c) Malvern Results

The Malvern data generated from analysis of each of the granulating solutions used in the effect of a surfactant upon the process of fluidised bed granulation are shown in Table 5.2. The distance between the nozzle and the Malvern laser beam was kept constant at 200 mm for each determination. This corresponds to the distance between the nozzle and the surface of the fluidised powders within the bowl during the granule manufacture.

These results indicate that there is a reduction in $\bar{x}$ as the concentration of SLS in the granulating solution is increased. At the 7.5% $^{w}/v$ concentration however there is a slight increase in $\bar{x}$. This can be attributed to droplet coalescence and/or complete evaporation of very fine droplets. A narrow distribution i.e. larger w value is also obtained as SLS is added to the system. This value however remains fairly constant as the concentration of SLS is increased about 0.5%.

5.6.4 Estimation of the number of SLS molecules per square metre of surface of each of the sprays

Table 5.2 showed that increasing the concentration of sodium

Table 5.2. Malvern data for the atomised granulating solutions containing surfactant

% $^{w}/_{v}$ Sodium Lauryl Sulphate in granulating solution	Rosin-Rammler $\bar{x}$ (μm)	Rosin-Rammler dispersion coeff. w
0	43	1.9
0.5	37	2.1
1	34	2.1
2.5	31	2.2
5	31	2.2
7.5	34	2.1

lauryl sulphate in the solution being sprayed produced a significant reduction in the mean droplet size of the spray. For a given nozzle the mean droplet size is related to liquid surface tension, density and viscosity.

Various workers have shown the effect of these liquid properties upon atomisation (Dorman, 1952; Marshall, 1954; Fraser and Eisenklam, 1956) with Nukiyama and Tanasawa (1939) deriving an empirical equation from a number of experiments for the drop size produced from a twin fluid nozzle system:

$$d_s = \frac{585}{v}\sqrt{\frac{\gamma}{\rho_L}} + 597\left(\frac{\eta}{\sqrt{\gamma\rho_L}}\right)^{0.45}\left(\frac{1000}{j}\right)^{1.5}$$

where d_s = surface mean diameter of droplets, v = velocity of air relative to liquid at the nozzle exit, γ = surface tension liquid, ρ_L = liquid density, η = absolute viscosity and j = air/liquid volume ratio at the air and liquid orifice respectively.

Yet over the SLS concentration range used here, there is likely to be little difference in viscosity and density and only small

changes in surface tension of the bulk solution at concentrations above the critical micelle concentration (CMC) [approximately 0.1% w/v for SLS in 5% aqueous PVP].

However, during atomisation an extremely large area of air/liquid interface is generated; Table 5.3 shows this to be in the order of $25m^2$ for each 100 ml of solution. It is postulated that this area of new surface may be large enough to allow migration of sufficient SLS from micelles to the air/liquid interface to effectively reduce the concentration of the solution below the CMC i.e. to a point where the concentration of SLS molecules in the surface will be changing even though the bulk concentrations before atomisation (up to 7.5% w/v) are well above the normal critical micelle concentration.

If this is the case, it will mean that the droplets will have significantly different surface tensions and this in turn could explain the results of Table 5.2.

To test this hypothesis the total surface area generated by the atomisation of a 100ml volume of each spray was calculated from the Malvern droplet size distribution data. The number of molecules in 100 ml was then obtained from the product of Avogadros Number and the concentration of surfactant. This enabled the area available per SLS molecule at the surface of the droplet to be calculated. These values were compared with the theoretical area occupied by a molecule at the CMC. The theoretical area was obtained from the Gibbs Free Energy Equation. A summary of the various calculated values is displayed in Table 5.3 with a detailed account of their derivation given in Appendix VII.

The results show an increase in surface area generated by the addition of surfactant to the granulating solution. At this point it was considered that the addition of surfactant could result in a significant reduction in surface tension of the liquid thereby resulting in improving the degree of atomisation.

The area available per surfactant molecule decreases from 2.23×10^{-20} m^2 to 2.57×10^{-21} m^2 upto a concentration of 5% $^w/_v$ of solution. At a concentration of 7.5% $^w/_v$ however there is a slight increase in area to 1.59×10^{-21} m^2. This can possibly be explained by the coalescence of droplets and/or evaporation of small droplets at this concentration thus effectively producing a slightly lower calculated surface area from the Malvern data than was actually occurring at the nozzle.

Table 5.3 Calculation of the area available per sodium lauryl sulphate molecule at the atomised solutions liquid/air interface

% Sodium Lauryl Sulphate in spray	Area generated per 100 ml atomised solution. (m^2)	Number of Molecules in 100 ml solution	Area available per molecule at the air/liquid interface (m^2)
0	20.5	-	-
0.5	23.4	1.05×10^{21}	2.23×10^{-20}
1	25	2.09×10^{21}	1.2×10^{-20}
2.5	26.75	5.24×10^{21}	5.1×10^{-21}
5	26.75	1.04×10^{22}	2.57×10^{-21}
7.5	25	1.57×10^{22}	1.59×10^{-21}

The area occupied by each surfactant molecule at the CMC was calculated to be 2.13×10^{-19} m^2 (Appendix VII (iii)). Thus, the area available for each SLS molecule at the surface of the spray droplets (see Table 5.3 above) is less than that occupied by an SLS molecule at the air/liquid interface. Therefore there is insufficient room at the spray surfaces for all SLS molecules and some must remain in the bulk as micelles.

These data have therefore dismissed the postulation that the improved atomisation was caused by large changes in surface tension due to surface/liquid interface concentrations of surfactant molecules being below the CMC. However a slight reduction in surface tension does occur above the CMC (Appendix Fig. VII-1) with the values ranging from 43 mN m^{-1} for 0.5% to 37 mN m^{-1} for 7.5%. It is possible therefore that only small changes in surface tension could result in improved liquid atomisation. The influence of surfactant molecules and related surface chemistry effects upon granule quality are discussed in more detail in section 5.7.4.

In making a number of the above statements, it must be made clear that many assumptions are made in the calculations and the complex interaction between SLS and PVP at the surface must complicate the use of these fundamental relationships. The assumption that the surface concentration is the same as the surface excess concentration calculated from the Gibbs Free Energy equation is a commonly acceptable approximation.

5.7. DISCUSSION

As the experimental results have shown, the introduction of a surfactant, whether added directly to the powder mix or dissolved in the granulating solution, has a profound effect upon the physical properties of the granules produced with the FBG. These results can probably be best explained by considering the theoretically based model of a droplet multi-particle component which forms the foundation of nuclei formation and ultimately granule growth within the bed. The droplet component of this model is obviously important and this was best illustrated by the significant effect that the SLS had upon the spray characteristics when dissolved in the granulating solution. It is important to be able to relate the relationship between these droplet and spray effects with the resulting granules.

Incorporation of the surfactant greatly affected the physical parameters of the sprayed solution. These were manifested in:-

5.7.1 Reduced Spray Break-up Point

High concentrations of surfactant reduced the break up point of the atomised granulating solution. Fortunately in the FBG used in these experiments this had little effect, since the break up point of the 7.5% $^{w}/v$ spray solutions coincided with the surface of the fluidised bed of powders. However if the spray had broken up before reaching the powder bed then there could have been a significant effect upon the collisions between the droplets and powder particles. At the break up point there is a reduction in velocity of the droplets and this lack of energy may be of significant magnitude to influence the ability of the droplets to combine successfully and wet the individual fluidised powder particles.

5.7.2 Increased Spray Cone Diameter

The spray cone diameter increases with increased quantities of surfactant dissolved in the granulating solution. This improved atomisation can be related to the lowering of interfacial tension. The nearly threefold increase in area resulting from the solution containing a 7.5% $^{w}/v$ concentration of SLS offers a vastly increased probability of successful droplet particle collision. Such large increases in spray cone diameter may cause problems if the fluidised bed bowl diameter is exceeded since wetting would occur. The result of this would be powder build up on the sides of the walls causing fluidisation problems and eventually leading to gross over granulation.

5.7.3 Reduced Mean Droplet Size

The Rosin-Rammler mean droplet diameter ($\bar{x}$) decreases as the concentration of surfactant increases. This reduction from 43 to 31 μm corresponds with an increase in the mean particle size of the granule batches produced. The first critical assessment of the results seem initially to be contradictory to the results obtained in Chapter 4; notably that a coarser granule was produced from an atomised spray with a large mean droplet size. It was indicated that this was not a strong correlation and that the introduction of another component may exert another effect. In this case the introduction of a surfactant to the spray vastly improved the wetting capabilities of the droplets thus enabling more successful collisions and ultimately improved granule growth.

There was also an increase in droplet population which would increase the probability of successful droplet/powder particle collisions. The predominant factor is however the improved wettability due to the surfactant present i.e. as the concentration of surfactant dissolved in the granulating solution increases there are more SLS molecules per square metre at the droplet air/liquid interface which ultimately becomes the droplet/particle interface after collision.

5.7.4 Sodium lauryl sulphate molecule concentration at the air/liquid interface of the atomised spray

Addition of the surfactant to the granulating solution results in improved atomisation with large droplet surface areas being generated. Calculations in section 5.6.4 showed however that there were no major changes in surfactant molecule concentration at the air/liquid interface despite the increase in surface area. It is however considered that the presence of the monolayer of surfactant molecules at the liquid/air interface inhibits evaporation and also promotes spreading over the powder particle surface after collision. Several workers (Blokh et al, 1973; Fainerman and Shapiro, 1973; Kremnev et al, 1974) have shown that the addition of surfactant to an atomised solution significantly reduces the heat transfer rate from the droplets. Thus during granulation in the fluid bed, the volume of liquid in the droplet will be significantly less affected by evaporation. Additionally after collision with powder particles the liquid bridges formed

will remain at a high liquid level and optimum growth state. This also results in dissolution of powder into the liquid and after drying formation of supplementary solid bridges of crystallisation. Spreading of liquid over the powder particles after collision will also be promoted. This is of particular importance in hydrophobic systems and is attributed to an increase in cos θ at the solid/liquid interface. These aspects will be discussed more fully in Chapter 7.

5.7.5 Relationship between the method of surfactant addition to the fluidised system and the physical properties of the resulting granules

The results from the granule and tablet assessment in section 5.5.3 highlighted the fact that the method of administration of surfactant to the fluidised powders did have a slight effect . In general on a weight per weight basis, the surfactant when dissolved in the granulating solution gave granules with improved pharmaceutical properties than when added directly to the powder mix. It is perhaps easiest to explain this effect by considering individually the differences in the granule and tablet properties with the use of the theoretical model of nuclei/granule formation previously suggested.

5.7.6 Granule Properties

(a) Flow Rates through Orifice

The granules produced with the surfactant added via the granulating solution gave, on a weight per weight basis, improved flow rates. There are three possible explanations for this although the true effect is more likely to be due to a combination of these:-

(i) Slightly coarser granulations.

(ii) The improved spreading of the binder over the individual granule surface with the thin PVP/SLS film effectively giving improved intergranular lubrication. SLS has been used as a lubricant during compression (Cooper and Brecht, 1957).

(iii) Improved wetting resulting in a more spherical uniform granule therefore reducing possible interparticulate locking.

(b) Particle Size

The slightly improved particle size of the granulations is considered due to the improved atomisation levels as previously described together with instantaneous wetting by the SLS already in solution. In the case of the surfactant added directly to the powder mix improved wetting only occurs when the droplets collide with the excipient powder particles together with a surfactant particle. However if no surfactant particle is present during such a collision then the improved wetting due to the SLS does not occur. When a surfactant particle is present wetting only occurs as it goes into solution thus there is a slight lag time. During this period there is also solvent evaporation taking place with solid bridge formation as the granule grows. Thus it is possible that not all the SLS goes into solution prior to solid bridge formation.

5.7.7 Tablet Properties

(a) Crushing Strength

Tablets prepared from granules with surfactant dissolved in the granulating solution gave lower crushing strength values than the tablets prepared from granules with the surfactant added directly to the powder mix. This effect can be attributed to a combination of:-

(i) A weakening of the interparticulate solid PVP bridges within the granule structure due to the large amount of SLS molecules present. The surfactant added directly to the powder mix would not have been activated as quickly and therefore would not have formed a substantial part of the solid bridge.

(ii) The surfactant added in the granulating solution produces granules with a thin covering of PVP/surfactant. The surfactant acts as an intergranular lubricant thus when a diametral force is applied to the tablet there is a greater likelihood of failure (see Fig. 5.10). This failure may occur around the compressed granules within the tablet.

Both series of tablets also exhibited large reductions in crushing strength values for small concentrations of surfactant. At higher concentrations only small further reductions in crushing strength were exhibited.

(b) Dissolution

Overall there was no difference between the $t_{30}\%$ values of the tablets thereby indicating that dissolution is not affected by the method of administration, only by the amount of surfactant added.

5.8 CONCLUSION

The results in this chapter have confirmed the importance of the hydrophobicity of the powder mix and its effect upon the theoretical model of droplet/multiparticle nuclei formation and on subsequent granule growth. The addition of surfactant to such a system was shown to improve the granulation. It was further found that the addition of surfactant dissolved in the granulating solution gave slightly coarser granules with improved flow properties than those obtained by addition directly to the powder mix. This was considered to be due to the profound effect that the surfactant had upon the atomisation and subsequent characteristics of the generated spray.

It is felt that the above observations together with the conclusions drawn from Chapters 3 and 4 indicate the need for a detailed investigation into the basic mechanism of granulation occurring within the fluidised bed. To date very little work has been published on this subject. It is believed that the study of the fundamentals of this process will help solve the current problems associated with transfer of conventionally granulated formulae to the fluidised bed. A preliminary investigation into these mechanisms was made and is reported in Chapter 6 of this thesis.

CHAPTER 6

AN INVESTIGATION INTO THE GROWTH MECHANISM AND STRUCTURE OF GRANULES PREPARED BY FLUIDISED BED GRANULATION

CHAPTER 6

AN INVESTIGATION INTO THE GROWTH MECHANISM AND STRUCTURE OF GRANULES PREPARED BY FLUIDISED BED GRANULATION

6.1 INTRODUCTION AND SCOPE OF CHAPTER

Studies on the mechanism of granulation have been predominantly performed on pan and drum granulations in particle size ranges slightly greater than those normally used for pharmaceutical purposes. Because of the lack of sufficient fundamental and operational research, numerous different types of granulator design are based on empirical formulations. The fluidised bed granulator could be broadly classified within this context. There are however certain mechanisms which are independent of the granulation method and these have been previously discussed in Chapter 1.

In the previous three chapters the results have indicated the need for a closer investigation into the basic mechanisms involved in granule growth together with a study of granule structure. The conclusions drawn from the factorial experiment highlighted the need for a sufficient quantity of liquid to remain within the bed to aid the formation of a coarse granule. Results from the study in Chapter 4 into the spray characteristics of the atomised granulating solution revealed that the larger droplets did give a coarser final granule. This gives considerable support to the important role of the droplet during the collision with powder particles. The greater volume of liquid from a larger droplet will enable the multiparticulate/droplet component to reach a higher level of liquid bridge formation and the component, as such, will have greater resistance to the forces of attrition acting within the bed.

The physico-chemical nature of the powder particles, as already demonstrated in Chapter 5, is extremely important. If a hydrophobic excess is introduced into the system a low level of growth results presumably due to the inability to attain strong droplet/particulate

combinations i.e. there is a resistance to attain the high level of liquid bridge formation and therefore a large quantity of binder is needed to produce a strong aggregate. At the end of granulation in such a system the resulting granules will contain a higher than normal level of binder. This may have a significant effect upon their physical properties and ultimately their compression and release characteristics. It was indeed suggested earlier by Seager (1977) that the method of granule manufacture may greatly influence the distribution of PVP within the final granule and thus affect the resulting properties. Later with fellow workers Seager (1979) confirmed this to be the case. The manufacturing methods investigated were those of roller compaction, wet massing and spraying drying. However granules produced from fluidised bed granulation were not studied although it was considered that the results would be similar to those of wet granulation.

Thus the results of Chapters 3, 4, and 5 confirm the need for a closer look into the fundamental mechanisms involved, paying particular attention to the role of the binder in this process. However the study is complicated because the granulation is occurring in a fluidised state. There are few techniques available to instantaneously freeze the granulation and determine the distribution of binder and liquid. It is therefore considered imperative that a technique should be developed to easily and accurately monitor and record these distributions during the granulation.

It was envisaged that the early work in this Chapter would be devoted to fully developing such a monitoring technique. When this had been fully mastered it was then used to comprehensively investigate the basic growth mechanism and final granule structure during the manufacturing process within the fluidised bed. It is hoped to correlate these findings with the results obtained in the preceding Chapters and finally to postulate how this fundamental understanding of the process may benefit future powder formulations for processing within the Fluidised Bed Granulator.

6.2 BINDER TRACING

The ability to easily and quickly monitor the distribution and concentration of binder during granulation was considered to be

essential for the study into the mechanism of granule growth within the fluidised bed granulator. The position of the binder has been used to demonstrate solute migration. Ridgway and Rubinstein (1971 and 1974) monitored the distribution of binder by using controlled attrition of granules to obtain successive layers of powder which were subsequently analysed by infrared spectroscopy. The technique however is rather slow and a permanent immediate record of the distribution is not obtained. An optical technique was therefore considered essential so that permanent photographic records could be obtained. The use of radio-actively labelled binder molecules was considered although it was finally rejected due to the complexity of the technique and the possible health hazards involved during processing.

For many years immunologists have been able to chemically combine fluorescent dyes with proteins (including serum antibodies) and subsequently view them in microscopical preparations by fluorescent microscopy. The fluorescent dyes can be detected in much lower concentrations than ordinary dyes, and can be readily conjugated with serum proteins. This technique of fluorescencemicroscopy has already been applied in pharmaceutical technology by Johnson (1979) during the assessment of tetracycline (fluorescent under ultra violet light) distribution after mixing with spray dried lactose.

The conjugation of a suitable pharmaceutical binding agent with a fluorescent dye was therefore considered to be the technique of choice for the proposed study. The method offers the advantages of a permanent photographic record and suitable fluorescence with low concentrations present.

6.2.1 Binder-Fluorochrome Conjugation Process

Fluorescein isothiocyanate (FITC) was selected as the fluorochrome for this study. The procedure for preparing and purifying the PVP/FITC conjugate is given in section 2.5.

6.2.2 Pilot Conjugate Evaluation Study.

The objective of this pilot study was to assess the feasibility of the PVP-FITC conjugate in its proposed role as a tracer during

the investigation into the mechanism of granulation within the fluidised bed. A model system of glass ballottini spheres was selected to simulate inert, non-porous particles of uniform size, shape and surface area. Previous studies (Dingwall and Ismail, 1977) have used a similar system to assess uniformity of binder uptake by binary mixtures of glass spheres.

Method

Sufficient water was added to 1 g of freeze dried conjugate material to give a 5% w/v solution. Approximately 10 g of glass ballottini No. 11 (mean diameter 200 μm) were placed in a mortar. Small aliquots (1 ml) of conjugate solution were added with continuous mixing until a suitable granular mass was obtained. A small quantity of this mass was removed, carefully smeared onto a clean, glass microscope slide and observed by an incident light fluorescence technique using a Vickers fluorescence microscope as described in section 2.5.1.g. Photographic records were taken.

Results

Photographic records of the drying granulated ballottini sample are displayed in Fig. 6.1. From these photographs the various levels of liquid bridges can be distinguished, as suggested by Newitt and Conway-Jones (1958). Photograph a shows the Capillary state whilst b, c, d are equivalent to the Funicular state. The near Pendular state is displayed by e whilst photograph f shows the final dried ballottini. It should be noted that the sample at this final stage is a rigid, solid structure and thus shows the solid binder bridges of the PVP-FITC conjugate. The photograph also gives evidence that the binder forms a continuous coating over the surface of the glass spheres.

Unfortunately the technique does suffer from a slight drawback as displayed in Fig. 6.2. This photograph shows the results of over exposing the sample to ultraviolet light thus causing fluorescent fading during illumination. Primary illumination should therefore be avoided during initial microscopic examination and full exposure should be limited until a photographic record is taken.

One possible problem was noted from this work; FITC does require a small residual level of moisture in the test sample for fluorescence to occur. However, this is not considered to be a major fault of the technique since granules suitable for compression have enough residual moisture to maintain fluorescence.

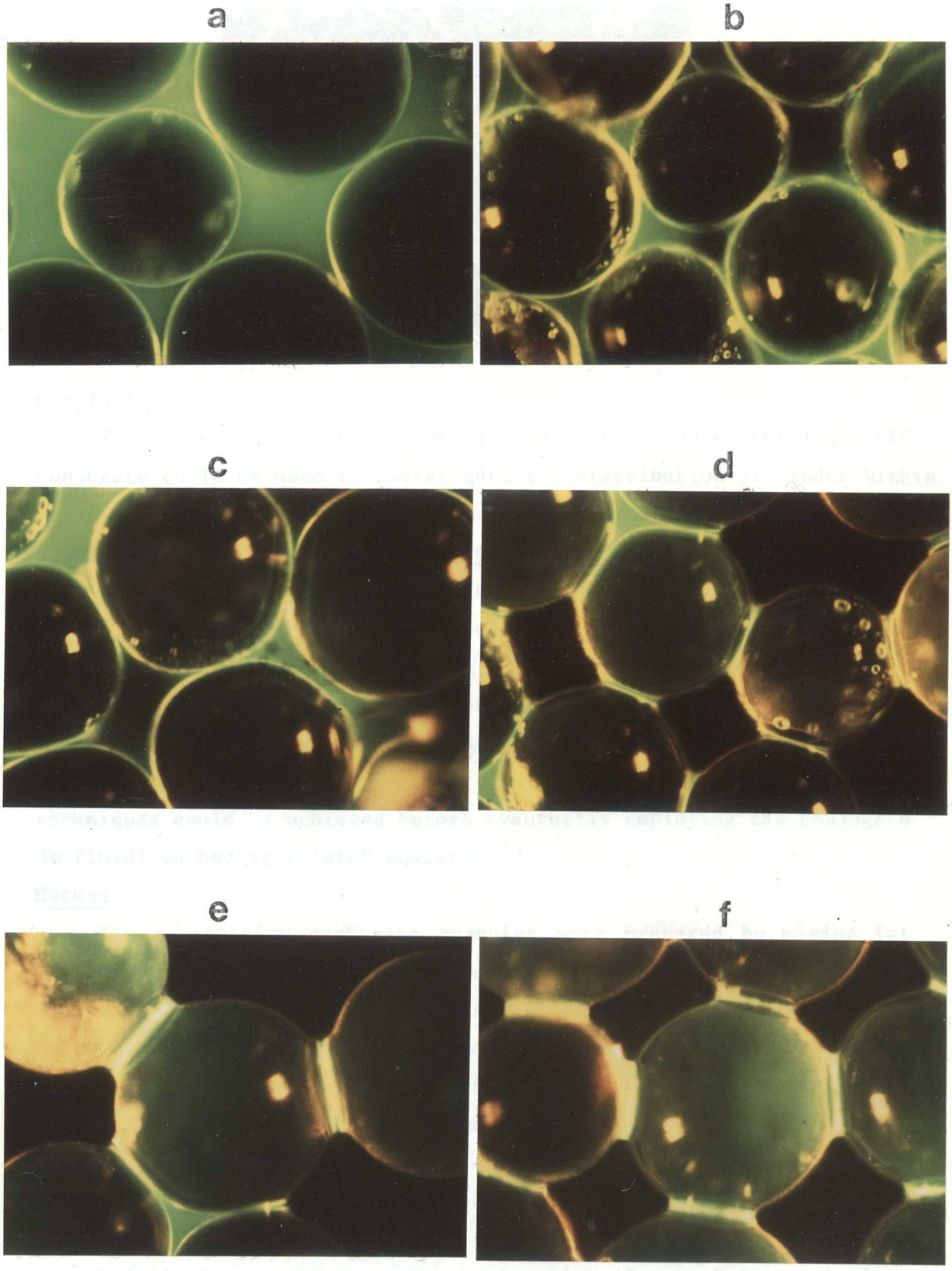
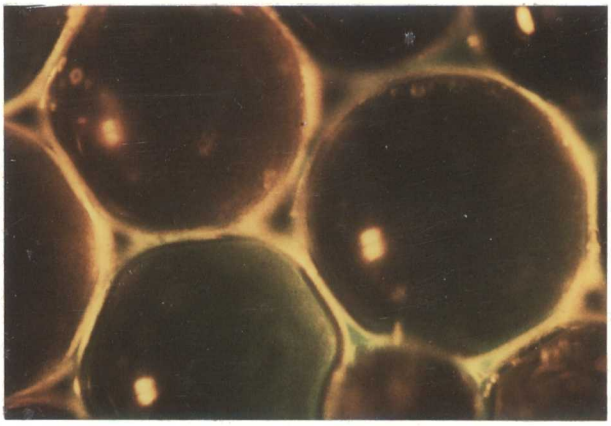


Fig. 6.1 Various stages during drying of a solution of the PVP-FITC conjugate around glass spheres. (magnification x 200)

Fig. 6.2 Over exposure to ultraviolet light of FITC-PVP conjugate (magnification x 200) showing loss of intense green colour.



Conclusion

The feasibility study showed conclusively that the PVP-FITC conjugate could be used to investigate the distribution of binder within a granule by monitoring the fluorescence using U.V. microscopy.

6.2.3 Conjugate Application to Granulated Powders

The application of the conjugate for use in powder granulations was initially assessed by the preparation of heavy magnesium carbonate granules using a traditional wet granulation technique. The distribution of PVP in a similar magnesium carbonate system, using controlled attrition, had previously been reported by Ridgway and Rubinstein (1971 and 1974). Therefore a direct correlation between both techniques could be achieved before eventually employing the conjugate in fluidised bed granulated powders.

Method

Heavy magnesium carbonate granules were prepared by mixing (at speed 1) 100 g of powder with 50 ml of a solution containing 5 g of PVP-FITC conjugate in a Kenwood Mixer (Model AE 125, $^{1}/4$ H.P.). The wet mass was passed through a 2 mm screen and dried in the fluidised bed for 120s at a drying temperature of 65°C. During this granulation, samples of granules were removed and processed in the following manner before viewing under fluorescent microscopy.

A. The final granules were mounted onto slides and viewed.

B. A sample was removed during the wet massing and plunged into liquid nitrogen to prevent any migration of granulating solution. The frozen granulate sample was then quickly immersed in molten paraffin wax, previously heated to 58°C, and immediately plunged into the liquid nitrogen. The embedded mass was microtomed into 20 μm slices which were carefully mounted on glass micro-

scope slides and viewed. The remaining exposed granule surface embedded in the main wax block was also viewed.

C. Dried granules were embedded in paraffin wax, microtomed and viewed as before.

Results/Observations

Photographic records of the magnesium carbonate granules showing distribution of PVP-FITC conjugate are displayed in Figs. 6.3, 6.4, 6.5. It is apparent from these three records that fluorescence can easily be identified and readily recorded.

The exposed surface of a microtomed granule previously plunged into liquid nitrogen and embedded in paraffin wax during wet massing is shown in Fig. 6.3. Uniform distribution of fluorescence can be observed, thus indicating good mixing at the end of the wet massing stage. Fig. 6.4 shows a microtomed slice of this granule. Again an overall distribution of fluorescence can be readily observed. However individual regions of intense fluorescence are clearly visible. This can possibly be explained by referring to the theoretical model of liquid within the interstices between the powder particles. At the end of granulation the granule will be in a Pendular state of liquid distribution. A 20 μm slice of the granule may well expose the various void spaces which have not been filled with granulating fluid. The distribution shown in this case by fluorescence would reflect this. Fig. 6.5 shows the distribution of fluorescence at the edge of a microtomed slice of a dried granule. There is a significant degree of fluorescence around the periphery of the granule which is evidence for solute migration, thus confirming the results obtained by Ridgway and Rubinstein (1971 and 1974).

When granules were sprinkled onto a glass slide and viewed, fluorescence was observed although only poor photographic records could be obtained due to the limitation of the depth of field at a suitably high magnification.

Conclusions

The results have shown that it is indeed possible to use the fluorescent nature of the PVP-FITC conjugate to identify the distribution of binder within a pharmaceutical system. Comparable binder distributions to those obtained by Ridgway and Rubinstein in a similar system have been displayed.

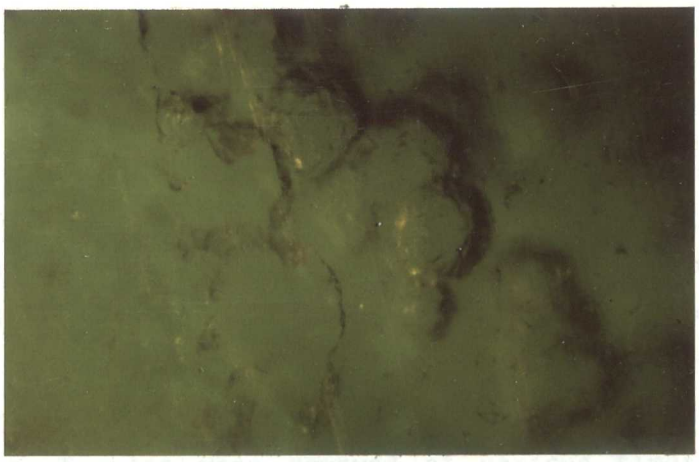


Fig. 6.3 Microtomed granule embedded in paraffin wax identifying uniform distribution of fluorescence. (magnification x 100)

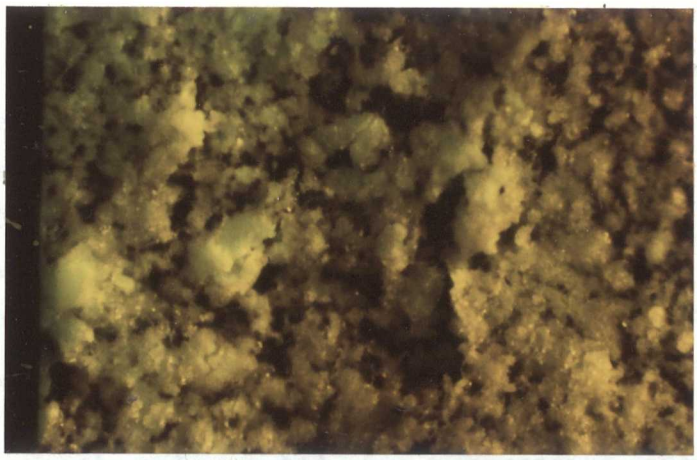


Fig. 6.4 Microtomed slice of granule showing overall distribution of fluorescence. (magnification x 50)

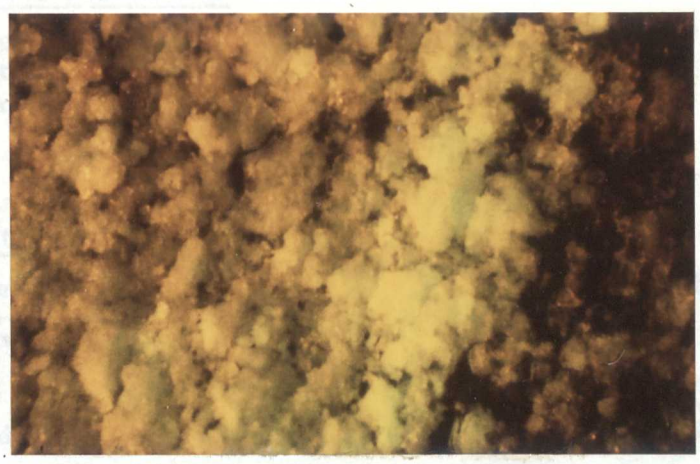


Fig. 6.5 Microtomed slice of granule showing fluorescence at edge of granule. (magnification x 50)

6.2.4 Examination of granules prepared by Fluidised Bed Granulation using the PVP-FITC conjugate

The application of the conjugate for investigating wet granulation proved to be successful. The technique was therefore used to investigate granule formation by means of binder distribution in fluidised bed granulated material. Several batches of each of three different powder mixes, representing various degrees of hydrophobicity, were granulated in the fluidised bed under identical processing conditions. Samples were removed at various times, treated as described in section 6.2.3, viewed under U.V. light and photographic records taken.

Method

The three powder mixes selected to represent various hydrophobic models were:-

(i) Lactose

(ii) 50/50 Lactose-Salicylic Acid

(iii) Salicylic Acid

Each powder mix was processed under the experimental conditions outlined in Table 6.1 with the method of granulation as described in section 5.2.1. Samples were removed during granulation. These were processed and mounted for microscopic examination utilising the methods outlined in section 6.2.3.

Results and Discussion

Photographic records of samples taken during each granulation are illustrated in the following section. The observed binder distributions are described and discussed below.

(i) Lactose

The observations recorded during the fluidised bed granulation of lactose with a solution of PVP-FITC conjugate are illustrated in Fig. 6.6. The initial study consisted of investigating the early stages of fluid addition. This was achieved by prematurely terminating the granulating stage after 1, 2 and 3 minutes and drying the powder under the conditions shown in Table 6.1. Samples were taken at two stages during this procedure. Firstly, *in situ*, at the end of the

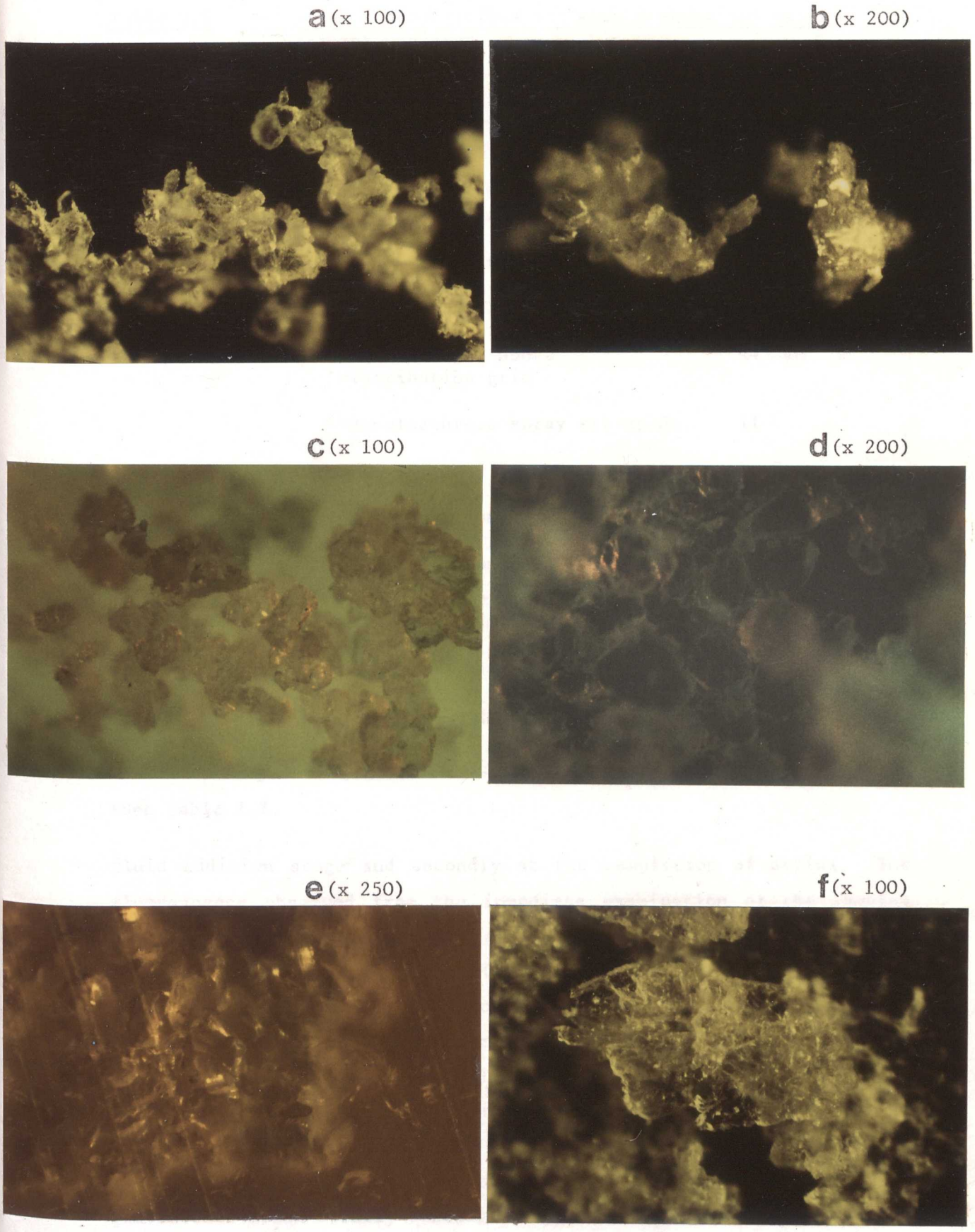


Fig. 6.6 Lactose granulated with PVP-FITC Conjugate, viewed under fluorescence microscopy. For details, see text.

Table 6.1 Optimised run conditions for each granulation using Fluorescent Conjugate

Stage	Parameter	Value
Granulation	Weight of powder charge	750 g
	Volume of 5% w/v PVP-FITC granulating solution added	Variable upto 200 ml
	Fluidising air temperature	50°C
	Fluidising air flow rate	$25 \times 10^{-3} m^3 s^{-1}$
	Nozzle height above distribution grid	445 mm
	*Manufacturers spray set up No.	11
	Atomising air pressure	1.67 bar
	Fluid addition pressure	1.4 bar
	Fluid addition rate	20 ml min^{-1}
Drying	Drying air temperature	65°C
	Drying air flow rate	$30 \times 10^{-3} m^3 s^{-1}$
	Temperature granulation dried to	40°C

*See Table 2.2.

fluid addition stage and secondly at the completion of drying. The fluorescence observed from the immediate examination of the samples removed at the end of the fluid addition stage clearly showed an even distribution on the surface of the lactose crystals with only a few concentrated areas of fluorescence. Evidence for this can be seen in photograph a. During these observations there was a suggestion of the particles beginning to form small agglomerates comprising of several crystals. This was indeed shown to be the case from the examination of the samples removed from the bulk of the granulator after drying. Small nuclei as illustrated in photograph b were identified with the fluorescent areas clearly distinguishable.

At the end of spraying 200 ml of conjugate solution, samples were removed without affecting fluidisation, immediately immersed in liquid nitrogen, mounted in wax, microtomed and viewed. A uniform distribution of fluorescence was observed. This is clearly evident from photograph c. Small areas of fluorescent fading can be identified as a yellow coloration. This is attributed to excessive sample exposure to U.V. light during photography. It should be noted however that, during initial sample viewing under U.V. light, fluorescence could be easily identified. Thus the yellow coloration surrounding the lactose crystals is evidence of binder distribution.

Samples removed and observed during the drying stage displayed surface fluorescence similar to that found from samples immediately removed after liquid addition. The fluorescence was however well defined. Evidence for this is shown in photograph d. Unfortunately the photograph was slightly underexposed to avoid fluorescent fading; although the distribution of binder can still be easily observed. Yellow areas (conjugate fluorescent fading) can be seen between lactose crystals and these are considered as being evidence of individual bonds.

Samples from the final dried granule mass were removed and either observed immediately or embedded in wax, microtomed and the various sections and core individually viewed. A view of a sliced granule embedded in wax is shown in photograph e. Individual areas of localised fluorescence can be easily identified. These are considered to be strong bonds of conjugate. A further less well defined fluorescence over the lactose crystal surfaces can be seen. The lactose granule shown in photograph e was viewed after drying (photograph f). Fluorescence was observed during the initial U.V. examination of the sample. However, a long exposure time during photography resulted in some fluorescent fading. A yellow/green coloration observed from the photograph is a true reflection of conjugate distribution. Fluorescence between individual granule crystals can be seen, together with several areas of intense fluorescence. This is an indication that the structure of fluidised bed granulated granules comprise mainly of solid binder bridges with little evidence of any solute migration to the periphery since no bonds of intense fluorescence at the surface of the larger granules examined could be found. (cf. magnesium carbonate, Fig. 6.5)

(ii) 50/50 Lactose/Salicylic Acid

An example recorded during the examination of the lactose/salicylic acid samples is displayed in Fig. 6.7. Examination of samples during the early stages of fluid addition showed nuclei formed by preferential combination of lactose crystals with fluorescence similar to that exhibited by the previously discussed lactose granulation. However further examination of samples removed nearer the end of fluid addition showed salicylic acid crystals adhering to the surface of the granule nucleus particularly between the interstices of the lactose crystals. A greater intensity of fluorescence seemed to be associated with the salicylic acid component, thus suggesting that hydrophobic material requires a greater quantity of binder to form aggregates during fluidised bed granulation. A further factor could be the absence of additional solid bridges to strengthen the interparticulate bonding particularly those of crystalline solid bridges. These would be more likely to play an important role with hydrophilic materials such as lactose.

(iii)Salicylic Acid

Very little or no fluorescence could be identified during the sample observation, particularly with the near dried material. This was attributed to the pH change caused by the salicylic acid which effectively suppressed fluorescence. A photographic record (Fig. 6.8) is included to illustrate this point.

Conclusion

The conjugate proved to be a useful tool to investigate the mechanism and the binder distribution during the fluidised bed granulation of lactose. Results suggested that the mechanism was similar to conventional wet granulation with no evidence of solute migration in the larger granules during the drying cycle. The method however suffered several drawbacks, notably that it was only useful for showing overall distributions of binder. It was also unsuccessful for investigating individual bond formation within granules. This was attributed to the limitations of the microscopic system since only a shallow depth of field is possible at the higher magnifications necessary for individual bond investigation. The technique unfortun-

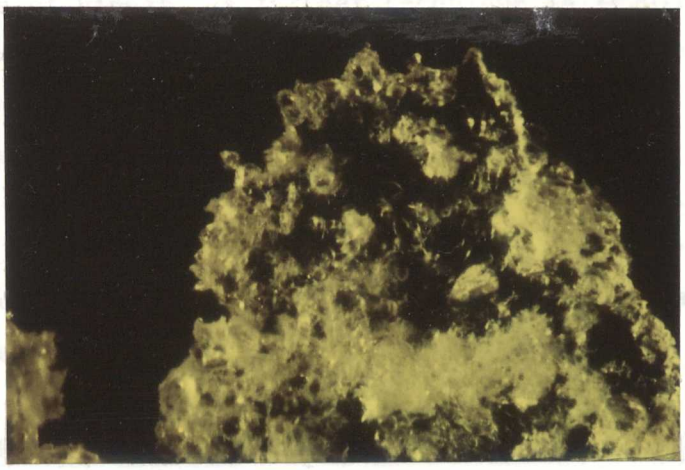


Fig. 6.7 Lactose/Salicylic acid granulation with fluorescence.
(magnification x50)

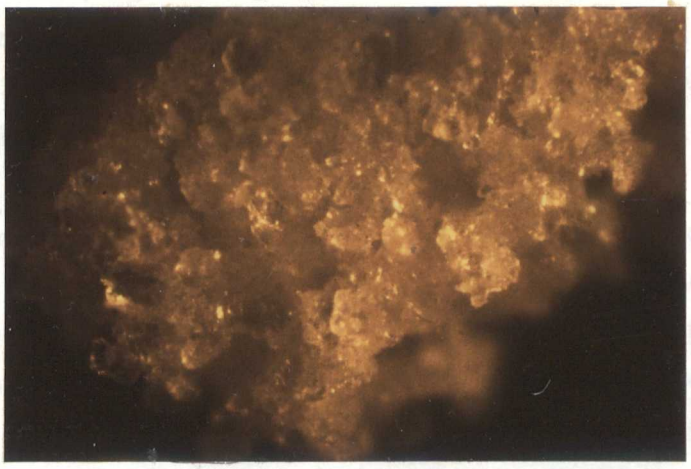


Fig. 6.8 Salicylic acid granule showing fluorescence fading.
(magnification x250)

ately proved to be unsuitable for salicylic acid granulations due to the localised acidic changes in pH resulting in fluorescent fading under UV examination.

To summarise: the fluorescent technique is suitable for certain materials and gives an overall general distribution of binder. It is a simple, direct method and possesses the advantage of immediate identification of binder. A further technique is required however for this study to yield the necessary information on binder distribution and granule structure in salicylic acid granulations. This is necessary to enable the basic, underlying fundamental mechanisms of fluidised bed granulation to be fully understood and used to explain the results acquired in the three preceding chapters. Scanning electron microscopy (SEM) was considered to be a more suitable way of achieving these aims.

6.3. AN INVESTIGATION INTO PARTICLE AGGREGATION IN A FLUIDISED BED AND FINAL GRANULE STRUCTURE.

A knowledge of particle aggregation and granule structure is considered essential to fully understand the process involved during fluidised bed granulation. Various authors have used the relationship between granule size and quantity of binder solution as a function for the cursory investigation of growth within the fluid. bed granulator. Ormós et al (1973a, 1975a)and Davies and Gloor (1972) demonstrated a direct relationship between granule size and quantity of binder with the former authors also reporting no effect upon size distribution. A linear correlation was observed by Shinoda et al (1976) between quantity of binder solutions and the logarithm of granule size. Other authors (Liske and Mobüs 1968; Wørts, 1972) however, have shown that there is a maximum granule size after which further addition of granulating solution does not produce an increase in growth. Schaefer and Wørts (1978c) attributed the above differences to the various experimental conditions used and attempted to elucidate the growth mechanism by studying the effects of changing process variables on the correlation between quantity of binder solution and granule size. Results were explained in terms of standard granulation theory. Further studies, using where necessary a more detailed, fundamental approach, are

considered essential. These will involve, in this work, the combination of sieve analysis data and scanning electron microscopy of several selected powder mixes.

Scanning electron microscopy has recently received much attention in pharmaceutical applications since it offers good sample definition and an excellent depth of field at high magnifications. Tablet surfaces have been monitored (Hess, 1978) whilst Seager et al (1979) and Ryder (1979) have used SEM to examine granule structure. The method is therefore considered to be ideal for the closer examination required during this study.

The present investigation will concentrate on a detailed examination of sieve analysis data generated from the premature termination of fluid addition during granulation of selected powder mixes. Samples of each of these granule batches will be subjected to detailed observation using scanning electron microscopy. A further technique for determining granule structure is also considered necessary and this will be achieved by solvent extraction. This consists of selecting a system which enables some of the excipients to be dissolved from an individual granule leaving the binder behind for more detailed examination. The system selected in this case will be salicylic acid and PVP since the former is soluble and the latter insoluble in ether.

The general overall conclusions derived from the above proposed investigation will be used for a final discussion to explain the findings from Chapters 3, 4 and 5.

6.3.1 Granulation conditions

Each powder mix was granulated in the FBG under the conditions shown in Table 6.1 using the method described in section 5.2.1.

For each powder mix the addition of granulating fluid was terminated after 2, 4, 6, 8 and 10 minutes corresponding to 40, 80, 120, 160 and 200 ml of granulating solution respectively. The wet mass was dried under the conditions as indicated in Table 6.1 but to a bowl temperature of 50°C. A fresh powder mix was used for each of these runs to avoid problems introduced by sampling and intermittent fluidisation. Granule growth curves were constructed using the data

generated from the 5 granulation times for each powder mix following particle size analysis by sieving. The sieving was performed as described in section 2.4.1. Samples of granules were examined by Scanning Electron Microscopy (see section 2.5.3).

6.3.2 Results and Discussion

(i) Lactose Granulation

The results of the sieve analysis for each of the granulations terminated at 2, 4, 6, 8 and 10 minutes are shown as histograms in Fig. 6.9. In the following diagram, Fig. 6.10, the progressive changes in the weight retained on each of four sieves is recorded to give a visual picture of the decrease in the amount of fines and increase in the amount of granular material as granulation progressed. This shows a rapid decrease in the amount of material less than 90μm. The material in the 90-180μm fraction increased up to about 5 minutes and then fell progressively as further agglomeration occurred; this is shown by a steady increase in the 180-354 and 354-710μm lines.

Scanning electron micrographs were taken of the lactose at 0, 2, 6, 8 and 10 minutes and representative SEM photographs are shown in Fig. 6.11.

Fig. 6.11a is a photograph of the original lactose crystals, i.e. at zero granulation time. It shows angular, flat faced crystals with a wide variation in particle size, the larger particles being characteristically triangular. This photograph is also useful for identification of lactose in later photographs.

After two minutes granulation, Fig. 6.11b, some of the smaller primary lactose particles can be seen to have adhered together. This trend is also reflected by the change in size distribution over this period. There is a reduction in <90μm material of about 25% and in <63μm material of 50%.

A peak in the histogram at the 125-180μm fraction is now differentiated.

Further agglomeration is seen in Fig. 6.11c, taken after 6 minutes, i.e. after the addition of 120 ml of granulating fluid. The larger particles are now taking part in the aggregation process. A marked reduction in the number of small particles is also evident from

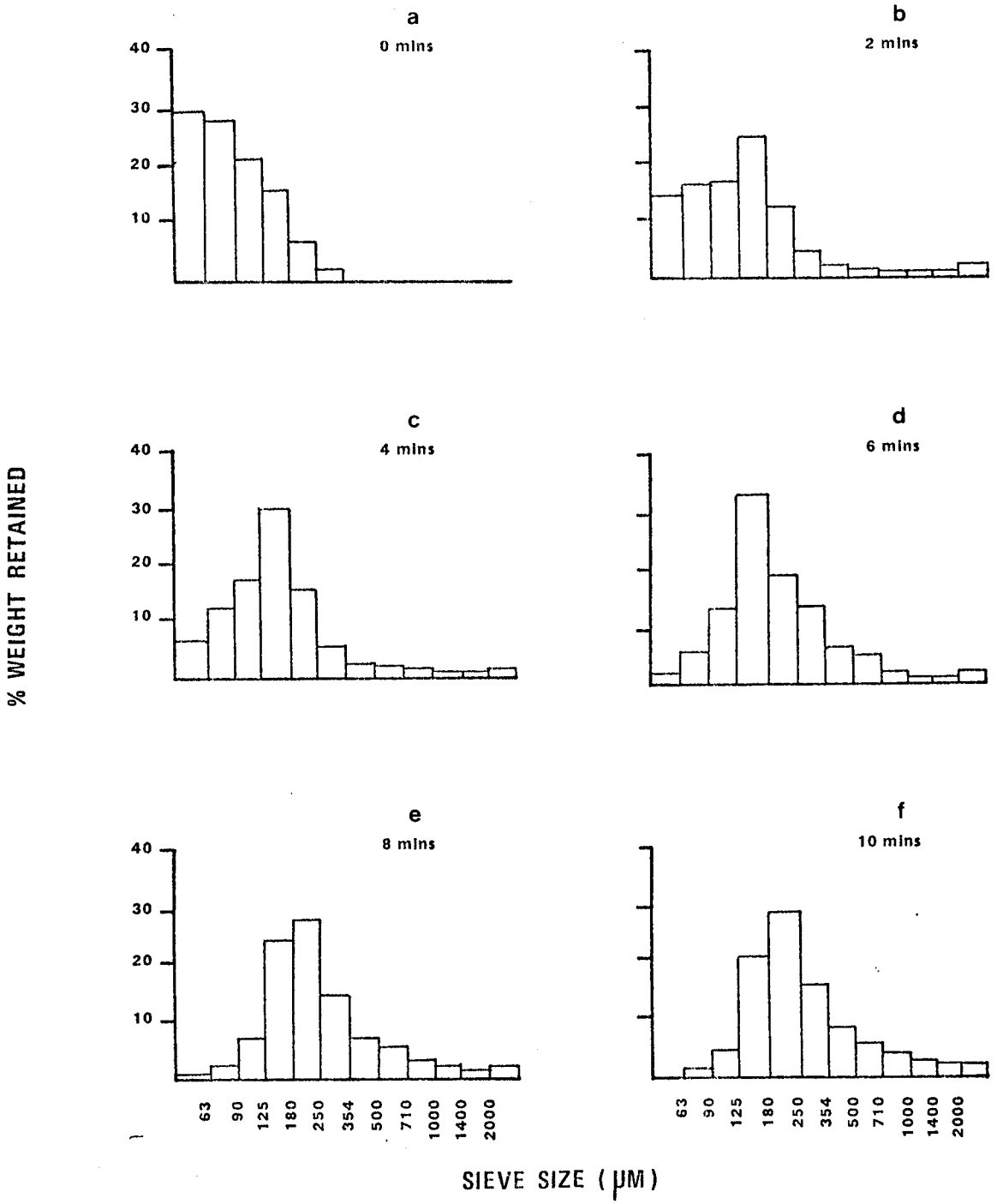


Fig. 6.9 Histograms representing sieve analysis data for Lactose granulation after additions of various amounts of granulating solution.

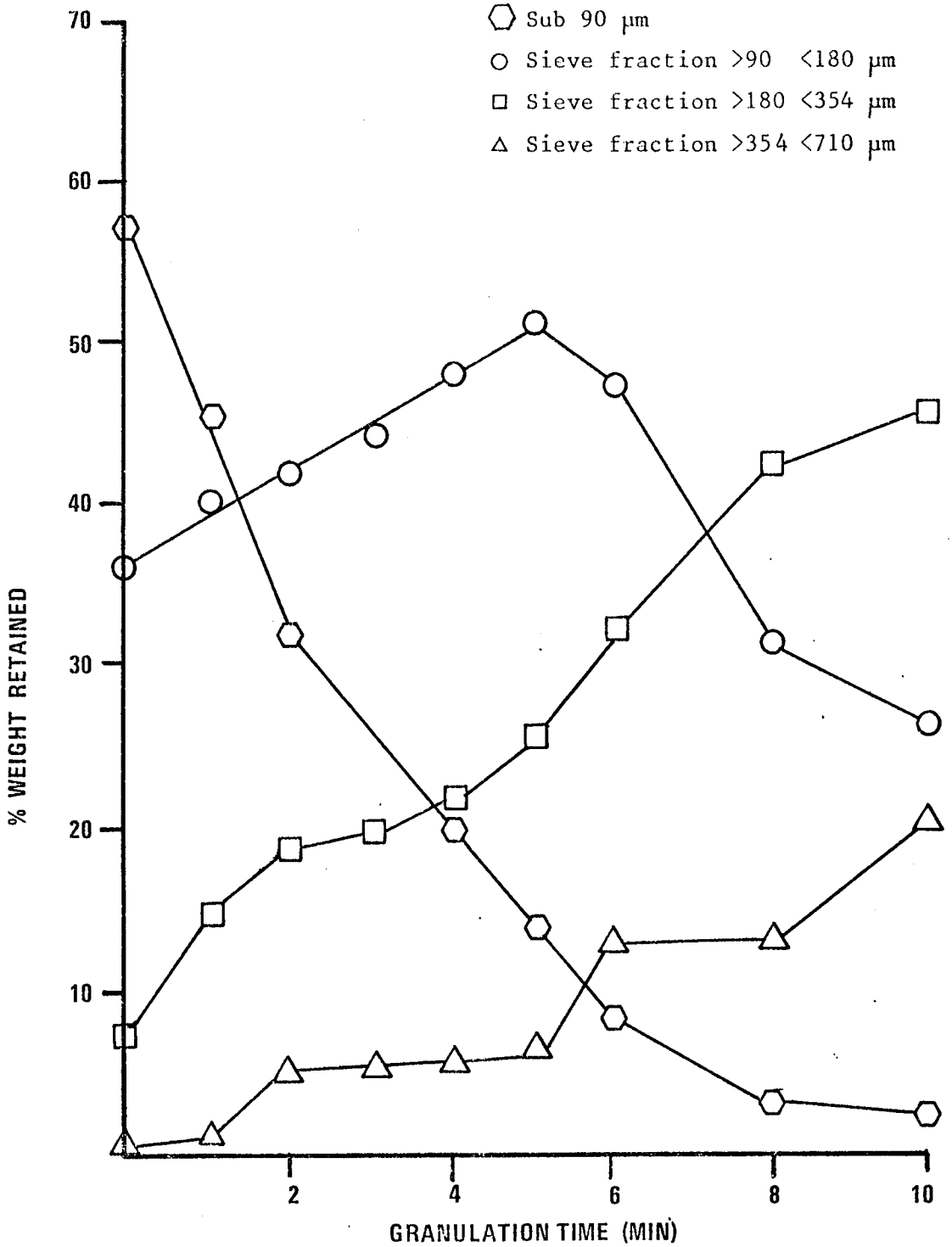


Fig. 6.10 Effect of increased quantity of granulating solution upon various sieve fractions of lactose granules.

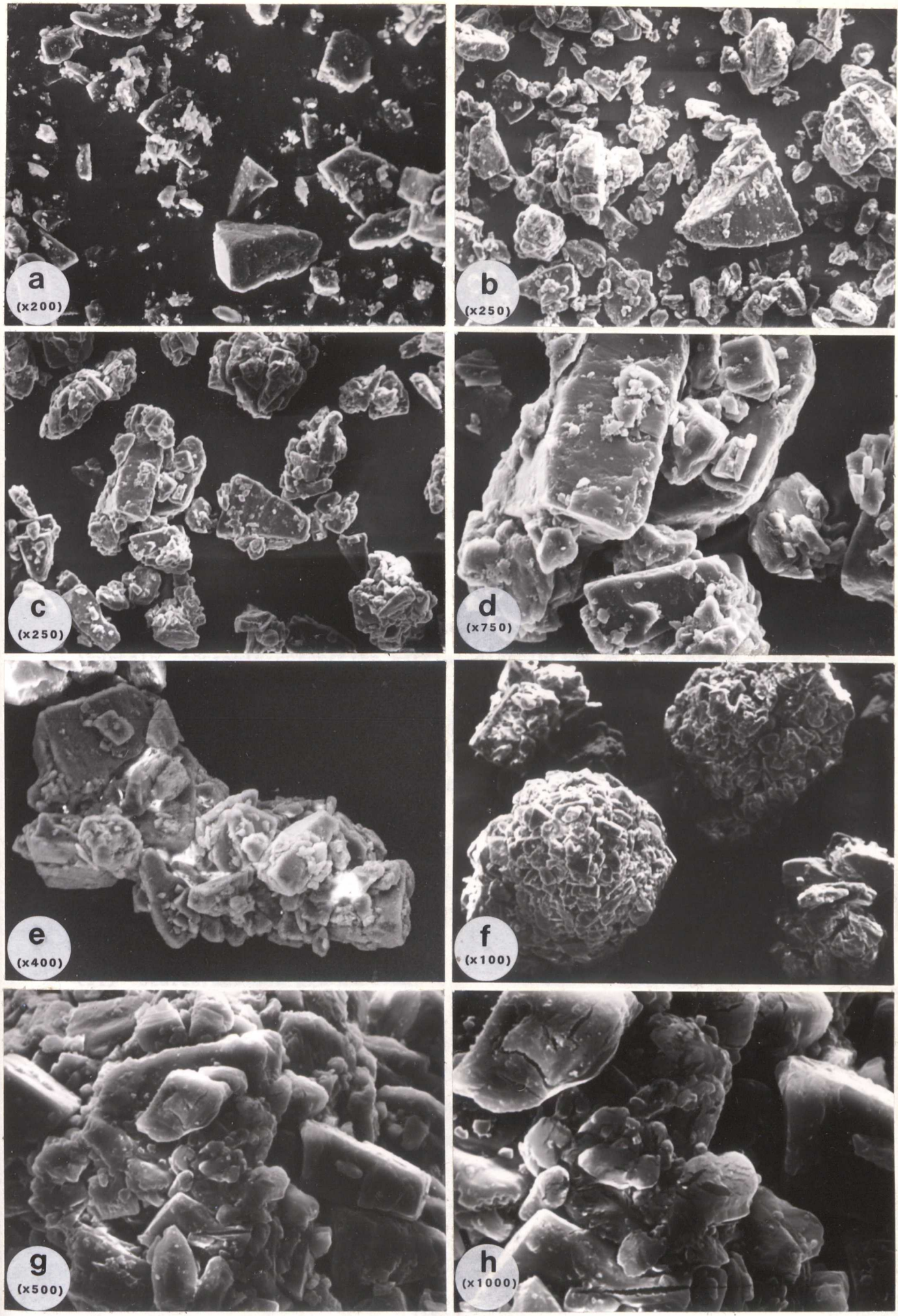


Fig. 6.11 Scanning Electron Micrographs showing various stages during granulation of Lactose. For details, see text.

the SEM. The size analysis shows that at six minutes there is 35% of the material between 125-180 μm and the skew in the distribution is now towards the larger size fraction (see Fig. 6.9d). This is also reflected in Fig. 6.10 by an increase in both the 90-180 and 180-354 μm fractions, although there is little increase yet in 354 - 710 μm granules. A high magnification of a typical granule is shown in Fig. 6.11d. It is interesting to observe here how the flat faces of adjacent lactose crystals have adhered together. An intermediate stage is shown in Fig. 6.11e after 8 minutes.

After 10 minutes the granules have now become markedly spherical (Fig. 6.11f) and tightly formed consisting of a large number of primary particles. The modal fraction has now moved to 180-250 μm (Fig. 6.9f). Between 6 and 10 minutes there is little further change in the amount of fines, but there is rapid increases in the 180-354 and 354-710 μm fractions (Fig 6.10). Over this period the amount of 90-180 μm material falls from 52 to 27%. A high magnification of one of these granules is shown in Fig. 6.11g. The crystals show evidence of a rounding off of the edges and corners of the angular lactose crystals, possibly suggesting partial dissolution at this stage. Fig. 6.11h is a greater magnification. At this scale it is possible to discern a thin layer of PVP over the surface of the individual crystals which has cracked in several places, probably during drying. Interparticulate bonds could not unfortunately be observed.

These changes in size distribution, coupled with the visual evidence enabled a tentative mechanism of fluidised bed granulation of lactose to be postulated. This is discussed in section 6.4.1.

(ii) Starch/Lactose granulation

A study of the starch/lactose (20 : 80) mix as used in Chapter 3 was carried out. Sieve analyses were performed at 2 minute intervals and the histograms are shown in Fig. 6.12. Progressive changes in the weight of material in four sieve fractions is shown in Fig. 6.13a and the overall change in mean particle size shown in Fig. 6.13b. A selection of SEM photographs for starch/lactose granulation are

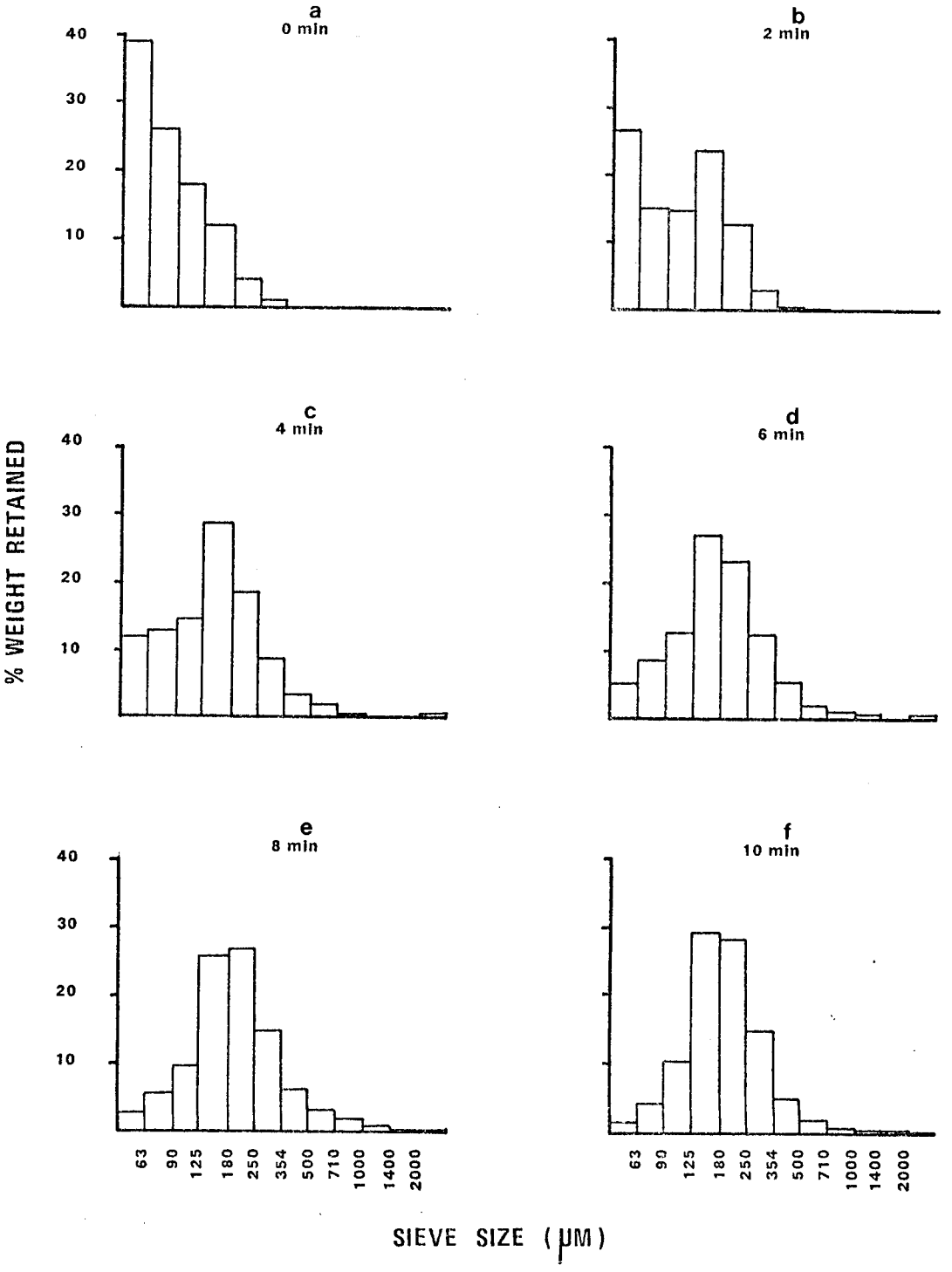
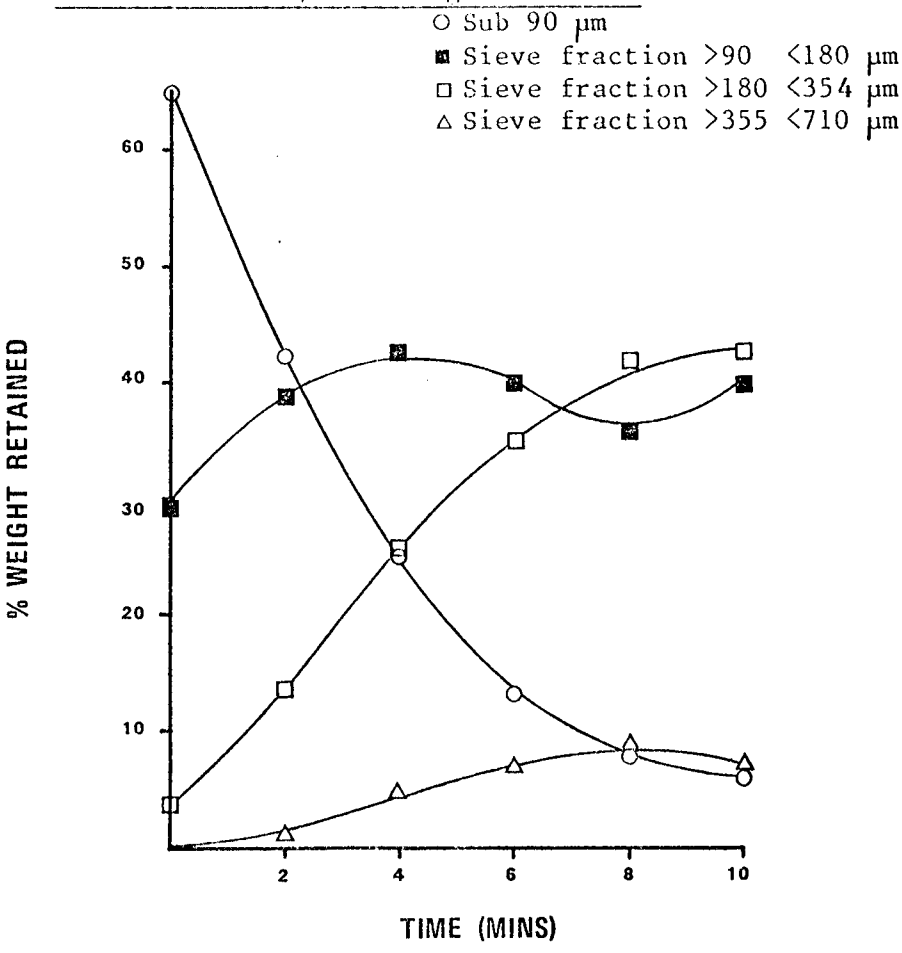


Fig. 6.12 Histograms respresenting sieve analysis data for starch/lactose granulations after additions of various amounts of granulating solution.

Fig. 6.13a Changes in weight retained for various sieve fractions with time for starch/lactose granulations.



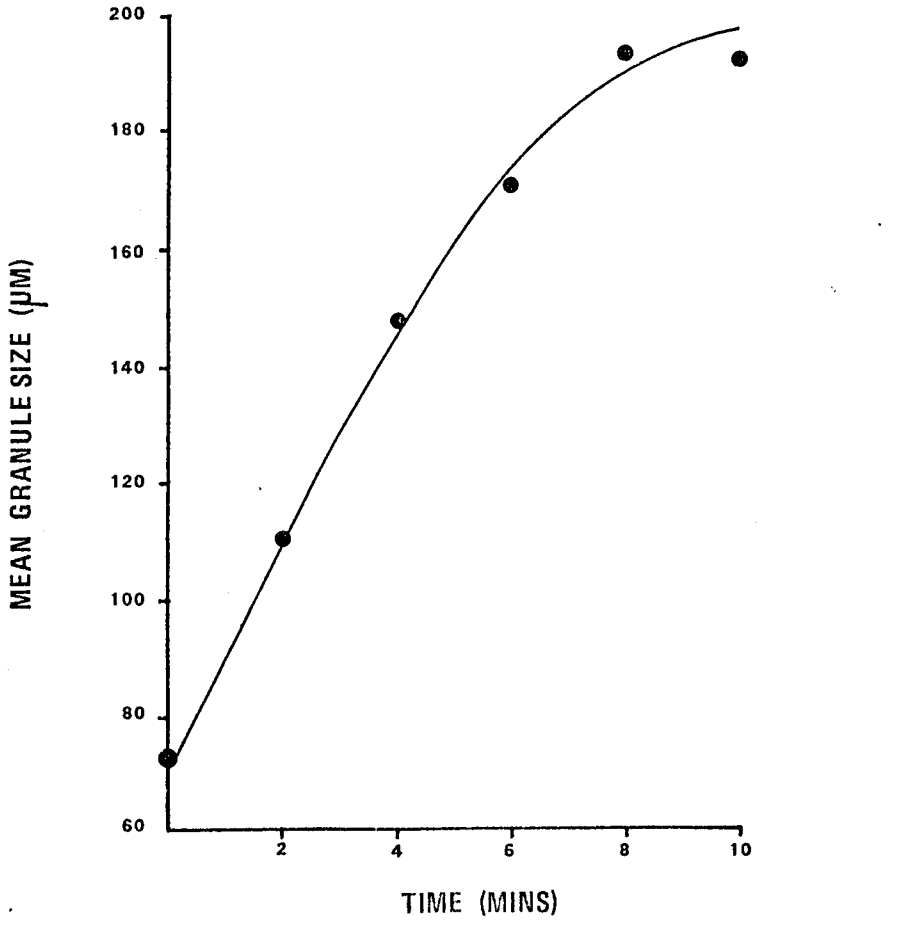


Fig. 6.13b. Change in mean particle size of starch/lactose granules with time.

shown in Fig. 6.14. A sequence of events will be outlined and related to this information. To aid identification of the particles in the SEMs in this series, a photograph of starch is shown in Fig. 6.14a. The spherical shape and narrow size distribution are characteristic and can be easily distinguished from lactose particles (Fig. 6.11a).

In the first 4 minutes of growth there is a reduction in sub 90μm material but an increase in all size fractions greater than this, particularly the 180-354 μm region. Indeed the rate of increase of this size fraction was almost identical to that observed for lactose alone over the same period. This possibly suggests that the initial nuclei in the starch/lactose granulations could be lactose/lactose, but on closer examination of the SEMs starch/starch clusters could also be discerned after a period of two minutes granulation (Fig. 6.14b). These units may, because of the cohesive nature of starch, have been present in the original powder. It is however possible that starch/lactose formations also existed.

Fig. 6.14c, taken after 4 minutes growth, shows that at this point the granules were heterogeneous mixtures of a few lactose crystals, plus many, smaller, starch particles.

A higher magnification of a 4 minute granule (Fig. 6.14d) shows the small, spherical starch particles adhering to the flat faces of the lactose crystals. But starch clusters can also be observed adhering to the granule. It is possible that these could have adhered as a complete unit.

After 6 minutes, the granule is taking on a spherical shape (Fig. 6.14e), which is fully developed at 8 minutes (Fig. 6.14f).

Referring to size changes between 4 and 8 minutes (Fig. 6.13a) it can be seen that the 180-354 and 354-710 μm fractions continued to increase, but there was a decrease in the amount of material between 90 and 180μm. The fines (<90μm) continued to be used up.

In contrast to the lactose granulation discussed previously there was no significant change in the size of the granules after 8 minutes This was reflected, not only in the mean particle size (Fig. 6.13b) but also in the individual fractions (6.13a). By this stage, it is suggested that the particles are sufficiently strong that further growth by breakage and subsequent layering does not occur to any significant degree under the process conditions used.

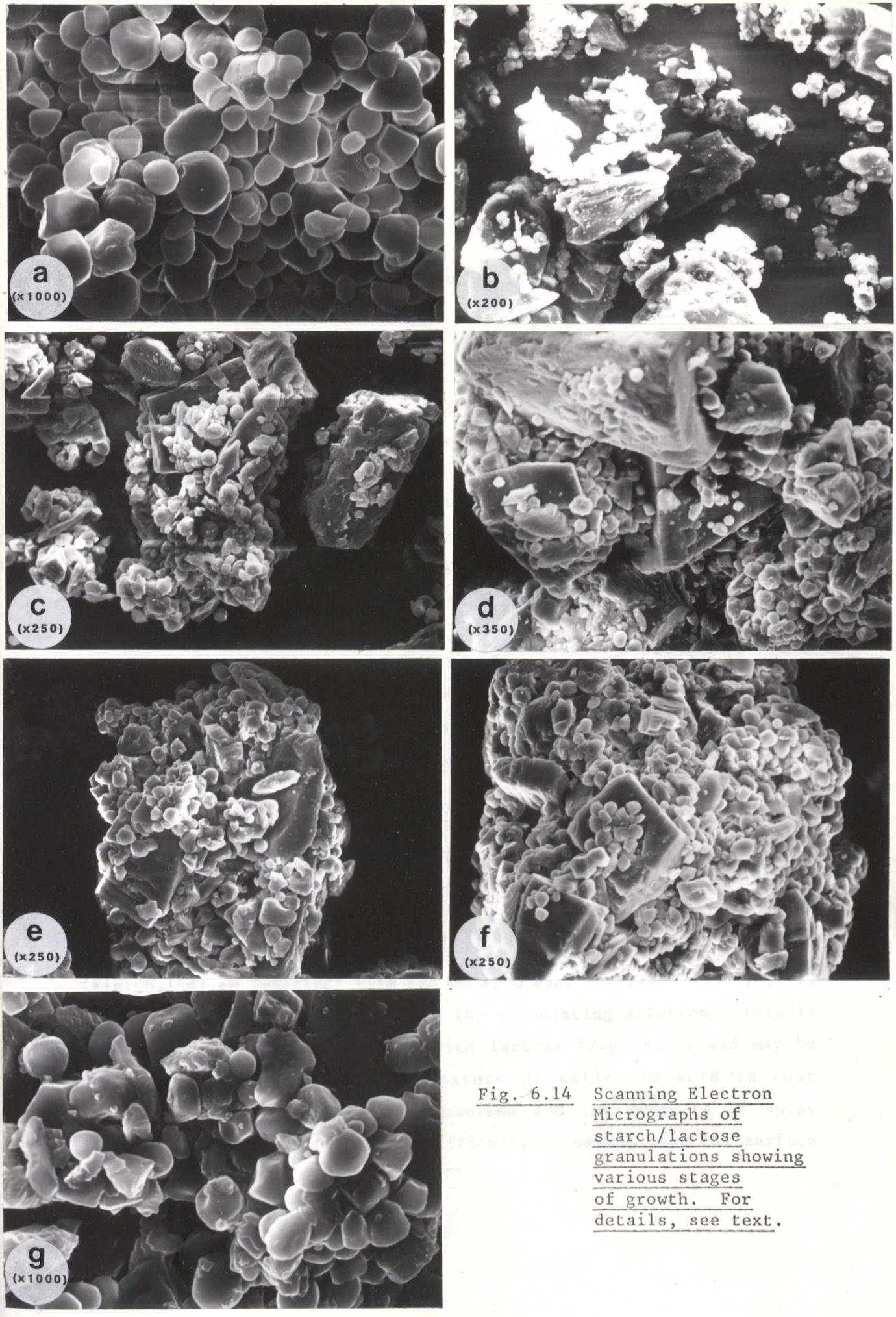


Fig. 6.14 Scanning Electron Micrographs of starch/lactose granulations showing various stages of growth. For details, see text.

This can possibly be explained by examination of Fig. 6.14f which illustrates how the small starch grains are collected within the angular spaces between the larger lactose crystals. This forms a close knit structure, with a large number of interparticular bonds some of which can be seen in Fig. 6.14g.

It is also interesting to speculate that the many starch grains wedged between the lactose crystals could explain the excellent disintegration properties of this formulation.

(iii) Salicylic Acid Granulation

Size evaluation of each batch of granules was attempted by sieve analysis. This proved to be extremely difficult due to blockage of the fine mesh sizes and the inherent agglomeration of the salicylic acid powder particles attributed to a static charge. Inaccuracy thus occurred during sieving and the data generated was considered to be of unsuitable quality for presentation. However with the use of SEM the structure of the salicylic acid granules could be readily observed. Photographs of the various batches are displayed in Fig. 6.15.

The overall shape and size of the powder particles is shown in photograph 6.15a. A certain degree of agglomeration is displayed by some of the particles. This is attributed to a possible electrostatic charge on the surface of the particles producing loose aggregates. Several larger particles are also present.

It was also impossible with salicylic acid to establish a granulation sequence. However a salicylic acid granule is shown in Fig. 6.15b. The lack of sphericity is typical of these granules (see an overall view in Fig. 6.15c). Note also the absence of fines in this granulation. On a high power photograph of the granule surface (Fig. 6.15d) an imperfect film can be seen over the crystals. This is PVP remaining after evaporation of the granulating solution. This is in contrast to the observations with lactose (Fig. 6.11) and may be indicative of the hydrophobic nature of salicylic acid in that the PVP solution has not been absorbed and the droplets of spray could possibly have had greater difficulty spreading over the surface of the crystals.

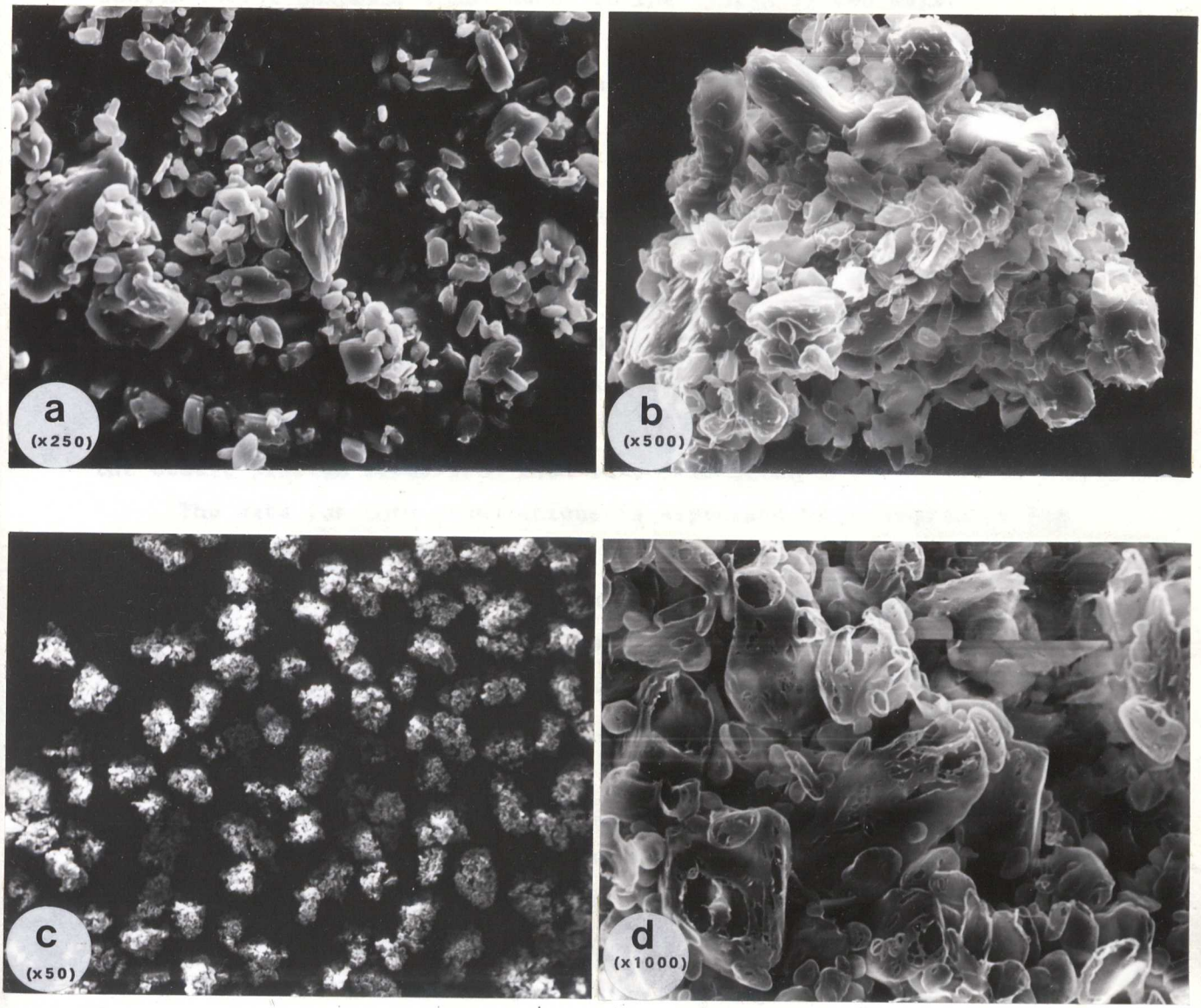


Fig 6.15 Scanning Electron Micrographs of Salicylic Acid granules. For details, see text.

(iv) Salicylic Acid with Sodium Lauryl Sulphate

Problems encountered during the granulation of hydrophobic powders and improvements achieved by the addition of a surfactant have been reported in Chapter 5.

Granulations of salicylic acid were now performed with the sodium lauryl sulphate (SLS) added to the system in two ways:

a) incorporated in the powder mix (7.5% w/w). For the sake of brevity this will be referred to as SLS(P) and

b) dissolved in the granulating solution (at a concentration of 7.5% w/v) (SLS(G)).

Improvement in the granulation process was such that there was sufficient size enlargement to enable accurate size analyses to be performed. It is possible too that the presence of SLS reduces the static problem associated with salicylic acid.

The data for both granulations is expressed by histogram in Fig. 6.16. Observations of this data shows that the granulation with surfactant added directly to the powder mix (Fig. 6.16a) produces a granulate with an approximately normal size distribution. This is in contrast to the results for SLS in the granulating solution (Fig. 6.16b) in which there is no clearly defined peak at the end of the fluid addition. Changes in mean particle size are shown in Fig. 6.17. A comparison between the individual sieve fractions gives a clearer understanding of the growth process. Comparative plots from each set of data for various sieve fractions have been constructed (Fig. 6.18). Representative SEMs are reproduced in Fig. 6.19.

The histograms in Fig. 6.16 reveal marked differences between the particle size distributions of granules produced by the two methods of SLS addition. At all time intervals SLS(P) produced a coarser granulation . Note for example the difference in the amount of material greater than 354μm at 10 minutes (Fig. 6.16) and the much larger proportion of finer material in the sample in which SLS was added to the granulating solution than when in the powder. These differences are also emphasised by the change in overall mean particle size with time shown in Fig. 6.17.

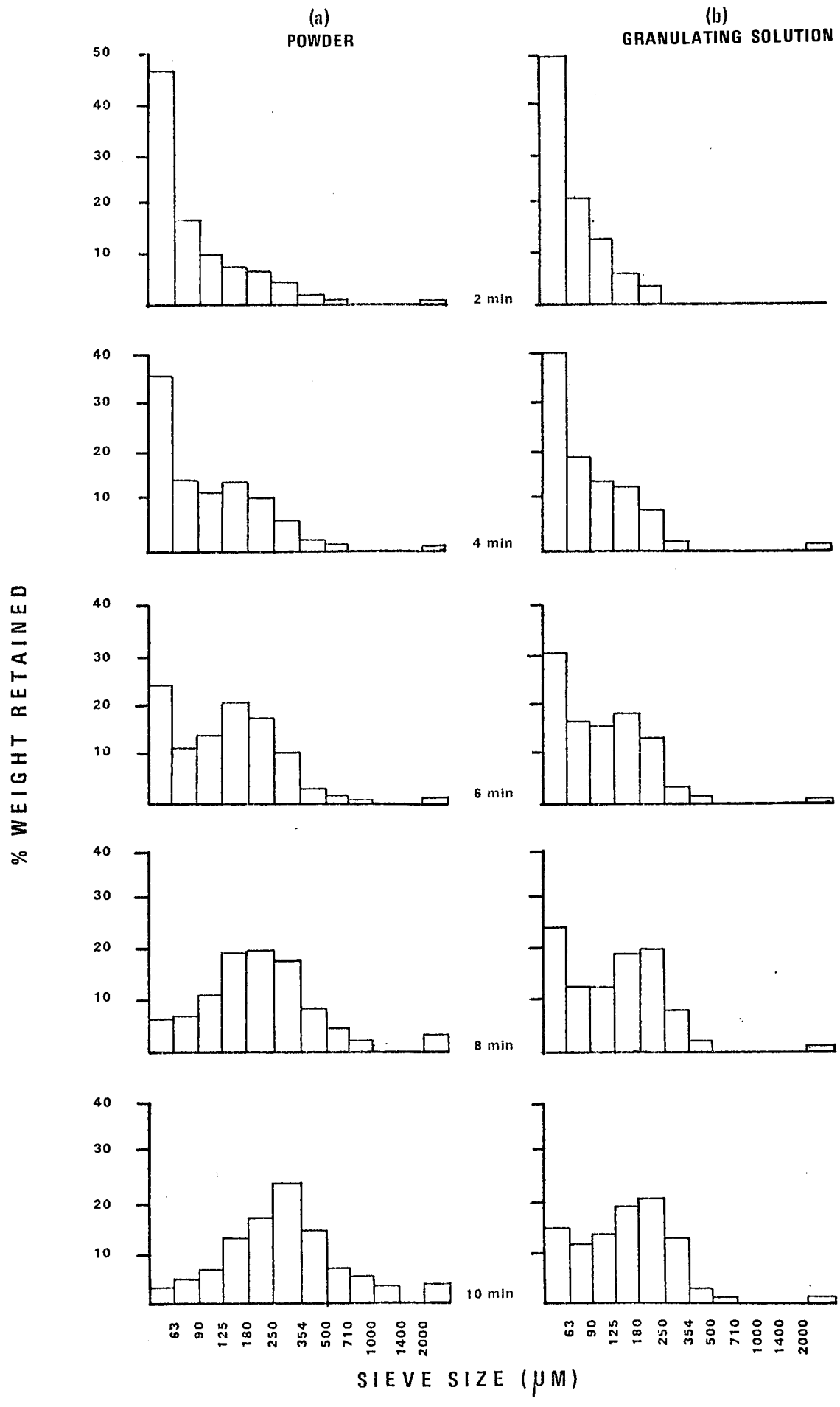


Fig. 6.16 Sieve analysis data of granules of salicylic acid with sodium lauryl sulphate(a) in powder and (b) in granulating solution.

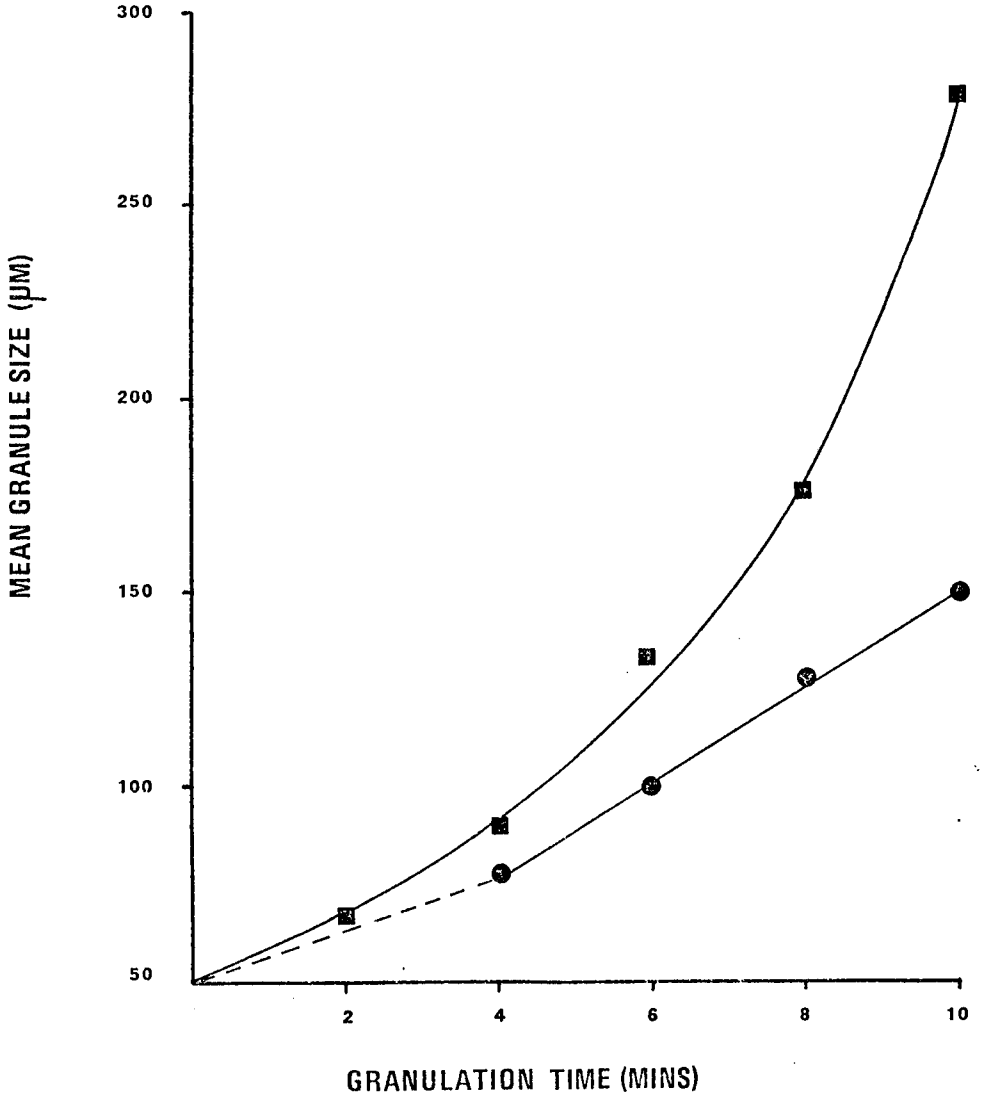


Fig. 6.17 Change in mean granule size with time for salicylic acid with sodium lauryl sulphate added directly to the powder mix (■) or dissolved in the granulating solution (●).

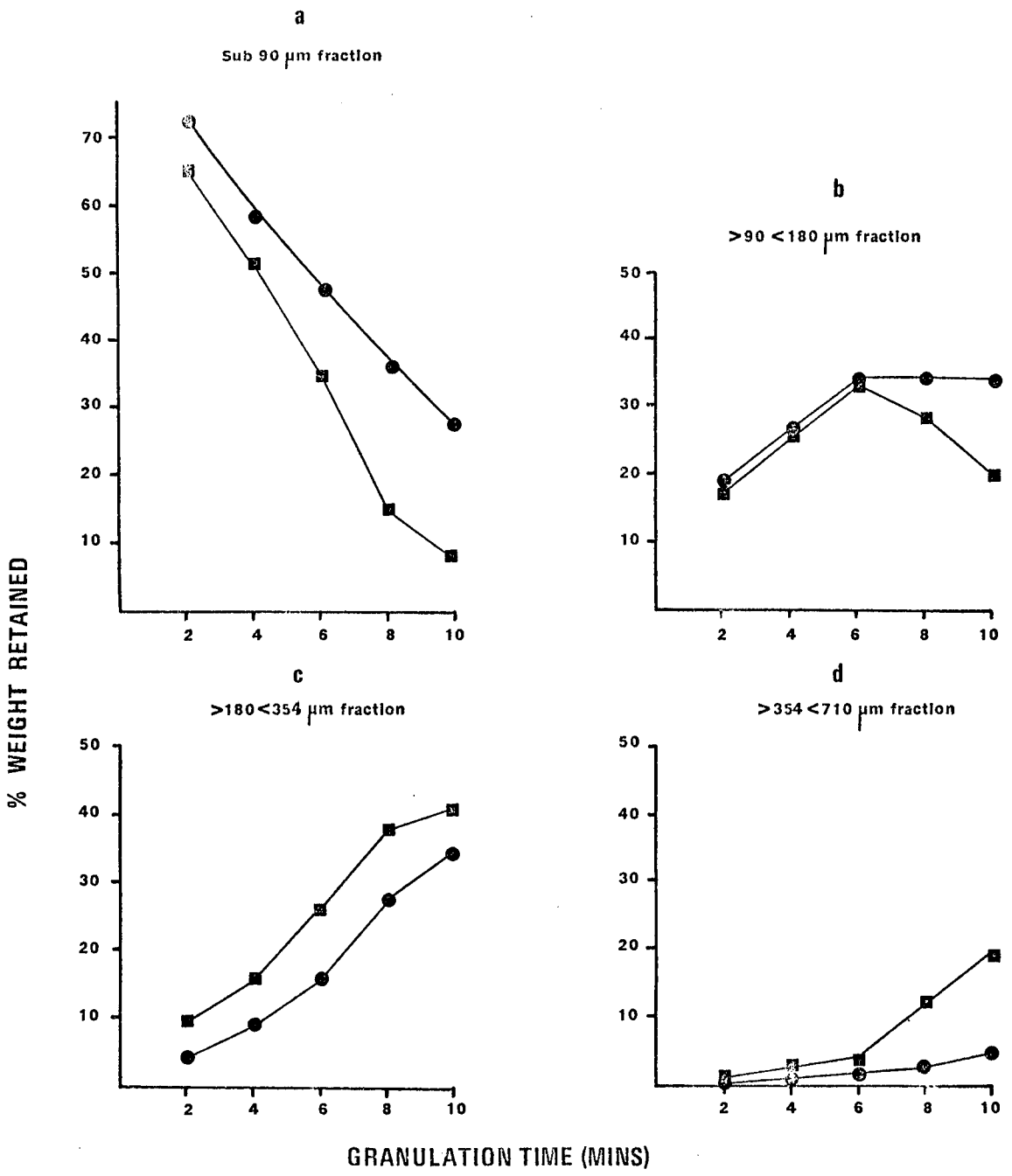


Fig. 6.18 Changes in weight retained for various sieve fractions for salicylic acid granules with sodium lauryl sulphate added directly to the powder mix (■) or dissolved in the granulating solution (●).

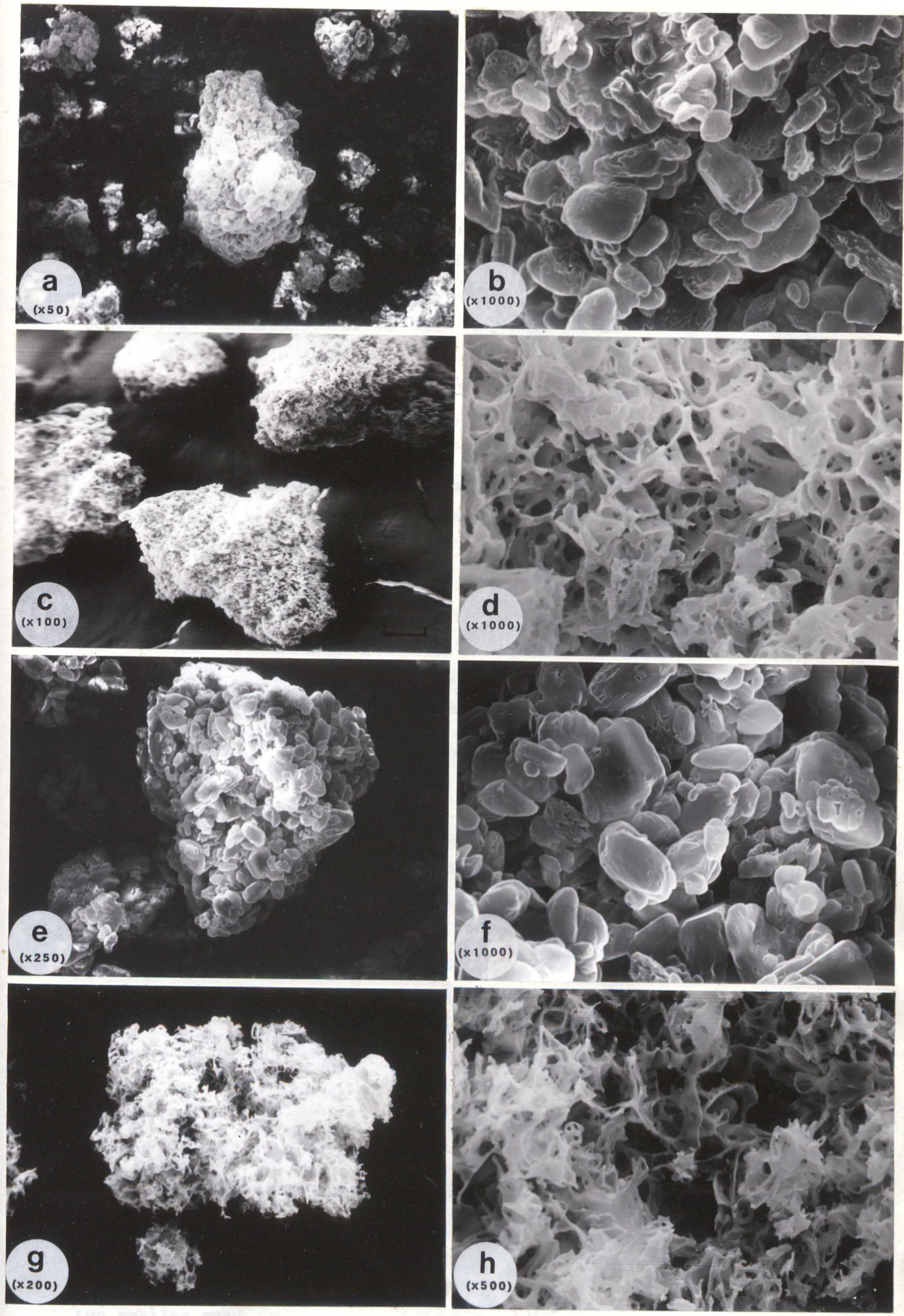


Fig. 6.19 Scanning Electron Micrographs of salicylic acid granules containing surfactant. PVP residues after solvent extraction are also shown (see text for details).

Examination of the changes in individual size fractions (Fig. 6.18) also gives further information. Initially, Fig. 6.18a shows that the reduction in fines (<90 μm) occurs at a greater rate with SLS(P). There is a greater proportion of larger granules 180 - 355 and 355-710μm (Fig. 6.18c and d) produced with SLS(P), particularly during the later stages of growth. This material is being produced not only from fines (Fig. 6.18a) but also from small agglomerates in the 90-180μm fraction (see Fig. 6.18b).

An indication of granule structure for salicylic acid granules containing surfactant can be seen in Fig. 6.19. Further insight can be gleaned by examining granules from which the salicylic acid has been extracted (see section 2.5.2) leaving just a binder shell. Distinct differences can be observed between the SLS(P) and SLS(G) granules.

Fig. 6.19a shows granules prepared with SLS(P) and this can be compared with an SLS(G) granule in Fig. 6.19e. In the latter the individual primary particles appear more distinctly. This is confirmed by looking at the high magnification photographs in Figs. 6.19b (SLS(P)) and 6.19f (SLS(G)). The SLS(P) granule appears to be covered with a layer of a substance which can be considered to be PVP/SLS. This coating is less distinct on the SLS(G) surface. The differences in this binder covering is clearly shown in the SEMs of the solvent extracted granules.

The extracted SLS(P) granule (Fig. 6.19c) is sponge-like in appearance with a more tightly formed structure. The consistency of the structure initially appears continuous throughout the granule suggesting that no, or little, solute migration had occurred. Closer examination however shows some localised areas of high intensity suggesting the addition of a near dried droplet of PVP solution. It has been suggested (Seager et al, 1980) that a high concentration of binder near the surface of the granule may improve compression properties. Fig. 6.19d shows the surface of this granule at higher magnification. The spaces in the matrix show where the original constituent salicylic acid crystals were situated before they were dissolved in the extraction process. Note the continuous film of binder around these crystals forming an envelope.

By contrast the extracted SLS(G) granules, see Figs. 6.19 g and h show a much more open structure. It is possible the low binder density in the central axis of the granule shown in Fig. 6.19g could indicate that this granule had recently been formed by the addition of two smaller ones.

(v) Lactose/Salicylic Acid 50:50 mix including addition of sodium lauryl sulphate

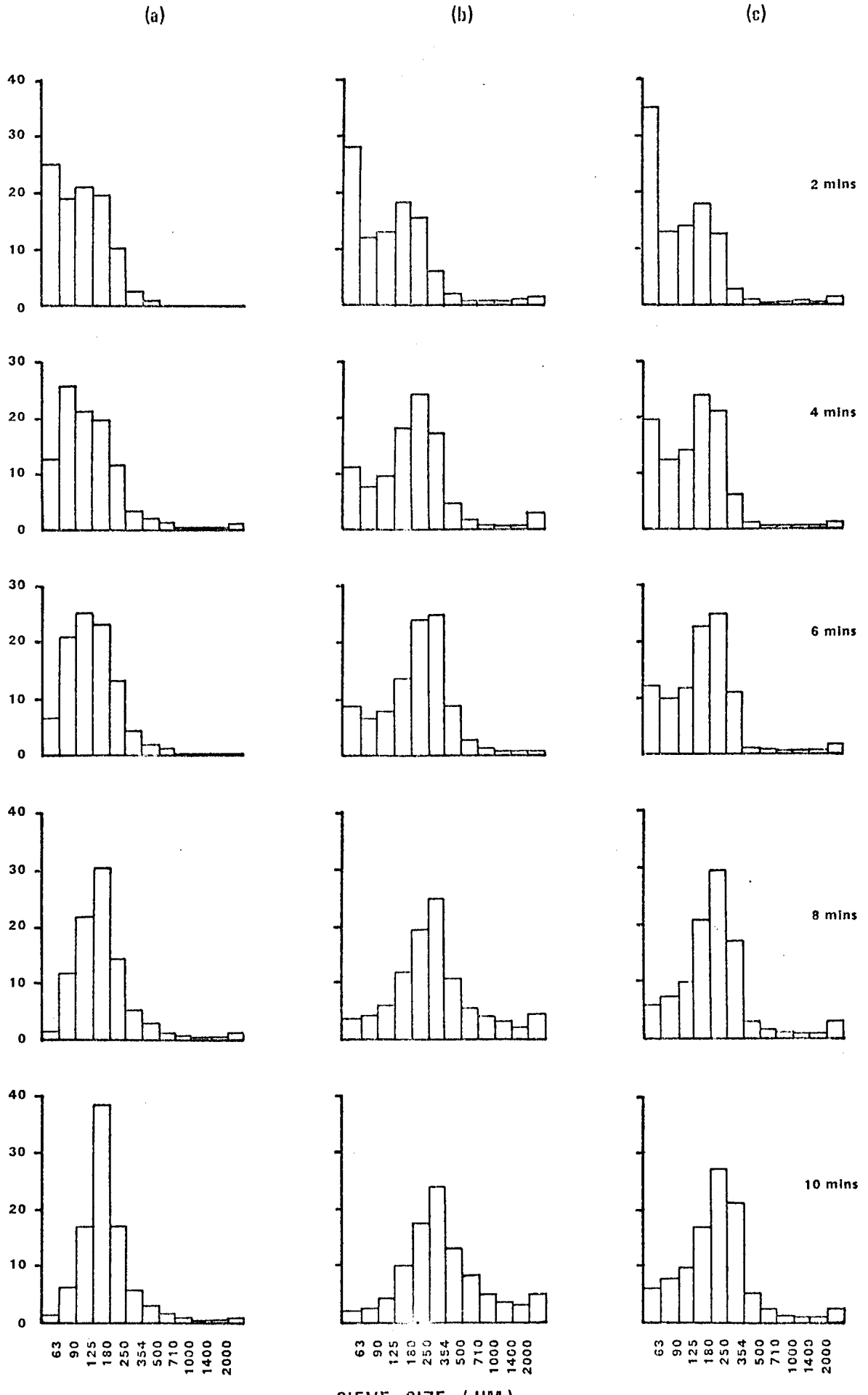
In Chapter 5 a 50:50 mix of Lactose/Salicylic Acid was used as a model system to investigate the influence of surfactants upon the process of fluidised bed granulation. This system was selected for further investigation as a model of a hydrophobic/hydrophilic combination which commonly occurs in pharmaceutical formulation. Initially the 50/50 mix alone was monitored and this was followed by an evaluation of the effect of surfactant addition to the system. Surfactant was added in the same manner as described in the previous section i.e. both in the powder (referred to as SLS(P)) and the granulating solution, SLS(G).

Data for all three granulations is expressed by Histograms in Fig. 6.20 enabling size distribution differences to be readily observed.

A comparison of the individual sieve fraction data for these three batches is displayed in Fig. 6.21. All three granulations exhibited a linear decrease in quantity of fines (i.e. <90μm) with increased time (Fig. 6.21a). The batch containing surfactant added directly to the mix displayed a greater decrease with only 4% total weight of granule remaining as fines after 10 minutes fluid addition. It is suggested that these remaining fines are a combination of particles which have become detached from agglomerates by collision during drying; interparticulate attrition resulting from the shaking action of the sieve shaker may also have produced some fine material.

Evaluation of the 90-180μm sieve fraction data (Fig. 6.21b) shows that there was a slow increase in the quantity of this fraction for the batch without surfactant. However the SLS(G) batch shows an initial increase from 32 to 38% of the total weight (from 2 to 4 minutes) followed by a gradual decrease, suggesting growth in a larger sieve fraction. The batch with surfactant added directly to the powder showed an immediate parallel decrease from 32 to 15%. This is in contrast to the results obtained with salicylic acid (Fig. 6.18) since the corresponding decrease did not occur until after 6 minutes fluid addition. It is suggested that this improved growth can be attributed to the preferential particle association of the hydrophilic fraction of the mix (lactose) caused by the improved wetting of the surfactant. Thus it would be expected that the core of the granule would be composed of lactose crystals then covered with salicylic acid crystals.

Fig. 6.20 Histograms of sieve analysis data for (a) lactose/salicylic granulations, (b) lactose/salicylic acid with sodium lauryl sulphate added in the powder mix and (c) lactose/salicylic acid with sodium lauryl sulphate dissolved in the granulating solution.



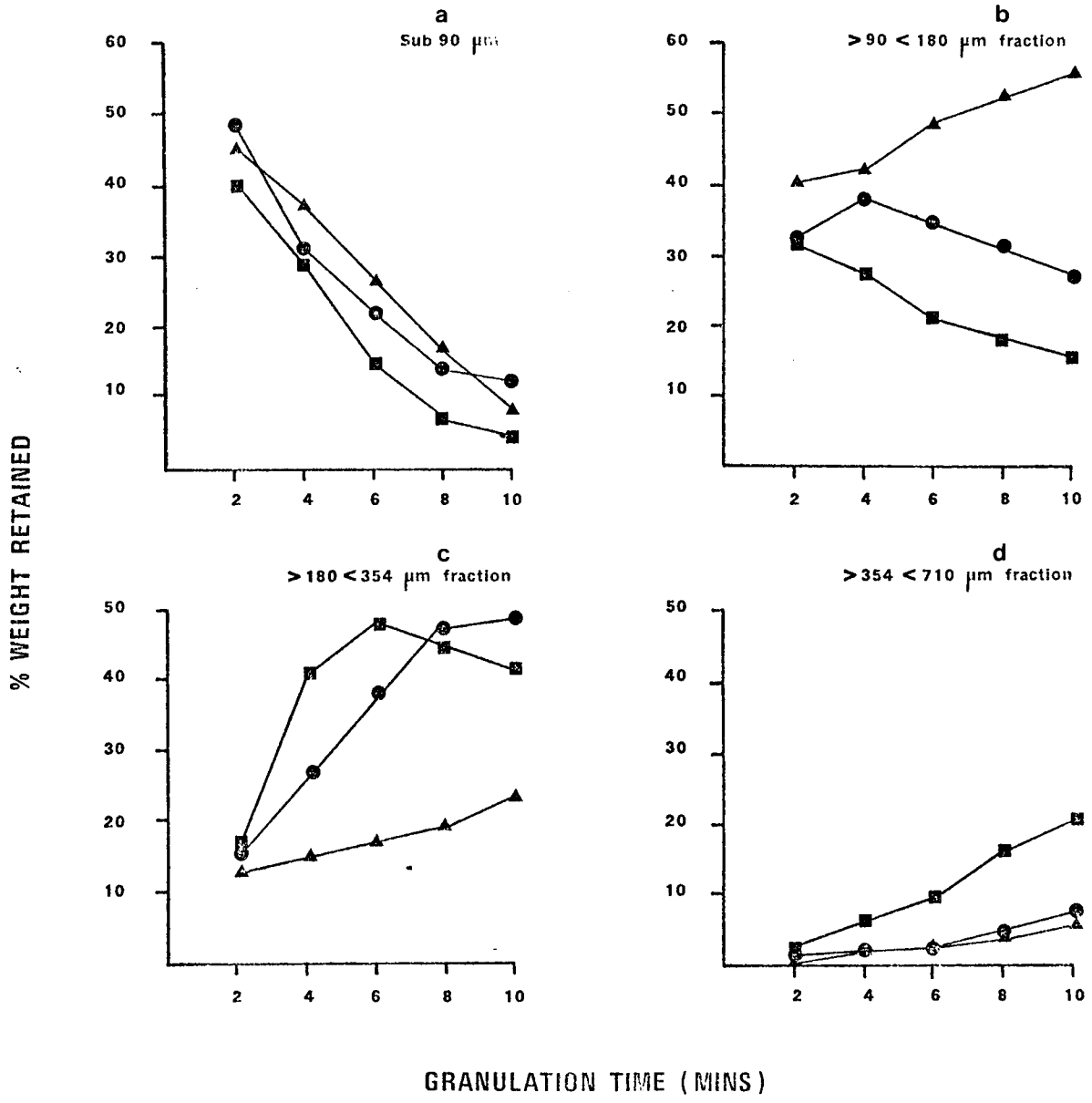


Fig. 6.21 Changes in weight retained for various sieve fractions for lactose/salicylic acid granulations (▲) together with sodium lauryl sulphate added to the powder mix (■) or dissolved in the granulating solution (●).

An examination of the data from the sieve fraction 180 - 354 μm (Fig. 6.21c) confirms the early period of intense growth in the batch containing surfactant added directly to the mix. Maximum growth in this fraction occurs after 6 minutes. A similar optimum growth occurs at 10 minutes when surfactant was added dissolved in the granulating solution.

The sieve data for the fraction 354-710 μm (Fig. 6.21d) shows that there is a linear increase in the amount of material in this size fraction with time. The batch containing surfactant added directly to the mix displays the biggest increase in size thus indicating the profound effect which the surfactant has upon particulate association.

An examination by SEM of all the batches aided interpretation of the sieve data. General conclusions were drawn from these observations. It is impossible to show all the photographic evidence from the scans, however the photographs worthy of further note to help explain major points are displayed in Figs. 6.22 and 6.23. Fig. 6.22 shows granules, both in original state and extracted, of lactose/salicylic acid granules and Fig. 6.23 shows lactose/salicylic acid granules prepared with the addition of sodium lauryl sulphate.

The results from a scan of a salicylic acid/lactose granulation sample (a) without surfactant addition shows the gradual build up of salicylic acid crystals on the surface of the larger lactose crystals (Fig. 6.22a-c). The large lactose crystals appear to be acting as the nuclei or substrate for the hydrophobic fraction. A similar result was postulated by Crooks and Schade (1978) who showed by chemical analysis of the larger sieve fractions that phenylbutazone was distributed over the outside of the granules. This was attributed to the increased wetting of the larger agglomerates which aided the adhesion of the smaller phenylbutazone particles.

Examination of the larger aggregates showed an uneven surface with individual particles difficult to identify (Fig. 6.22d).

After ether extraction, the lactose crystals and binder remain and the salicylic acid is dissolved. This is clearly seen in Figs. 6.22e-f. Note the strong PVP matrix between the large lactose crystals. Closer examination of 6.22f shows the craters remaining after dissolution of salicylic acid. Similar in structure to the starch/lactose crystals, the salicylic acid appeared to have in-filled the gaps and angles between the angular lactose crystals.

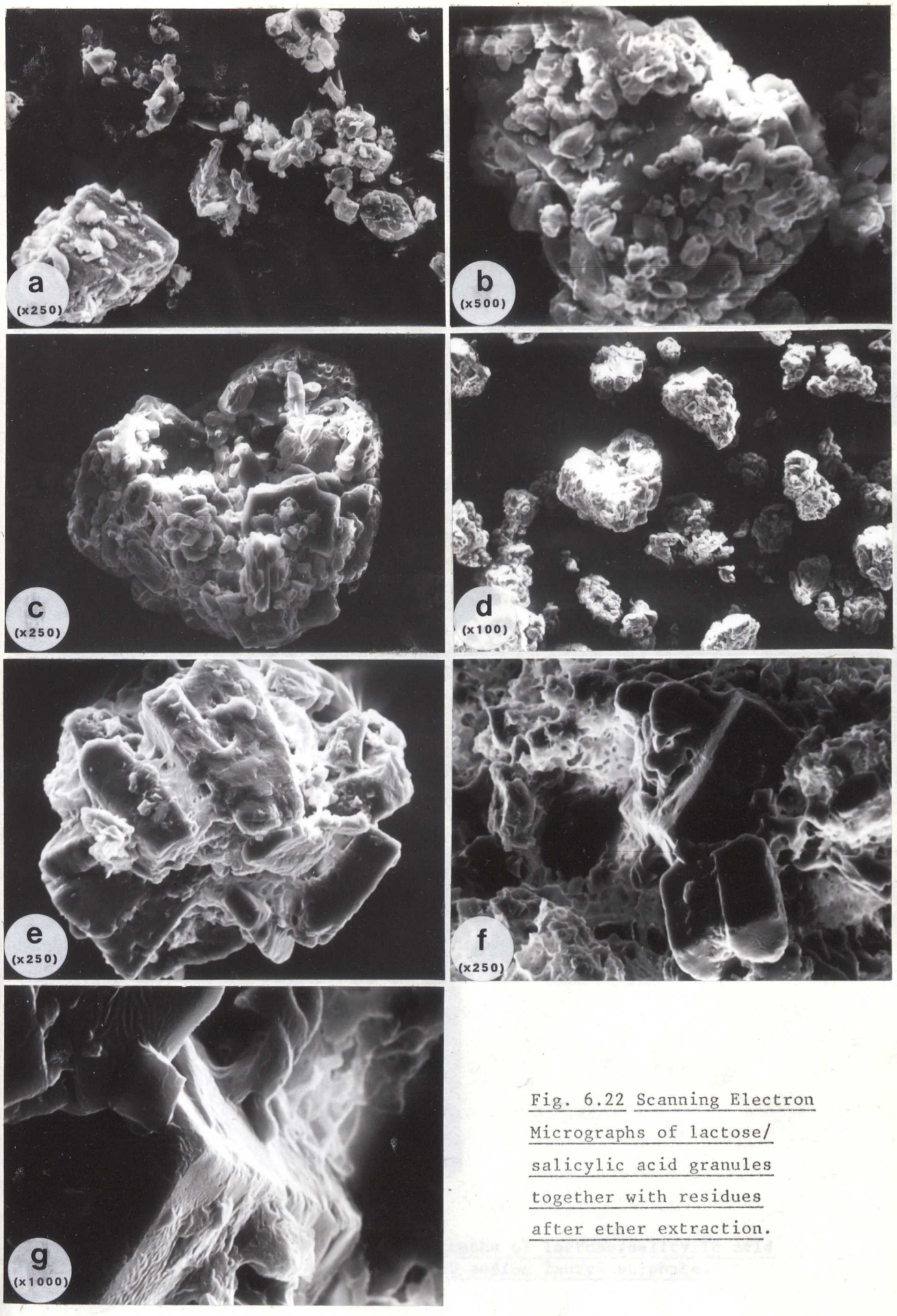


Fig. 6.22 Scanning Electron Micrographs of lactose/ salicylic acid granules together with residues after ether extraction.

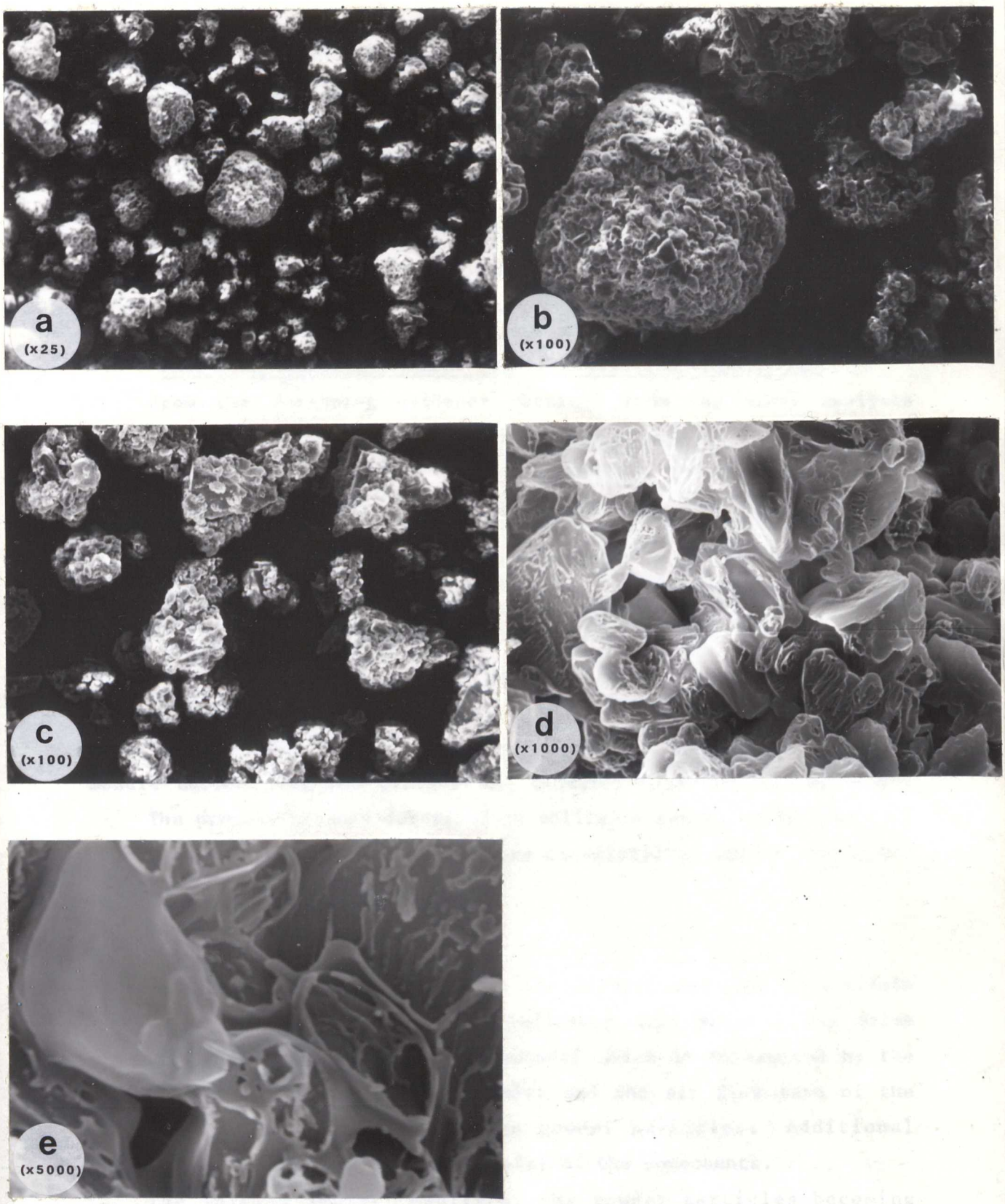


Fig. 6.23 Scanning Electron Micrographs of lactose/salicylic acid granules with addition of sodium lauryl sulphate.

The highly magnified area in Fig. 6.22g shows the actual binding of the PVP to a large lactose crystal.

The appearance of the granules prepared with surfactant after 10 minutes fluid addition are worthy of discussion (Figs. 6.23). The appearance of the granule after 10 minutes growth is shown in Figs. 6.23a and b for SLS (P). The granules are highly compact and spherical. The relatively more open structure of the SLS(G) granules can again be seen in Fig. 6.23 c and d. The film of PVP can easily be observed (Fig. 6.23d) over the surface of the crystals. A closer look at the surface (Fig. 6.23e) can distinguish solid binder bonds and the detailed structure of the binder can be seen.

6.4 PROPOSED GROWTH MECHANISMS FOR FLUIDISED BED GRANULATION

From the foregoing evidence obtained from the sieve analyses and scanning electron microscopy of various stages of the granulation process, it was possible to postulate mechanisms for the agglomeration and growth within a fluidised bed. These proposed mechanisms are presented below and compared with the well-established mechanism of conventional wet granulation.

6.4.1 Theoretical Considerations

The most important step in granule formation in the fluidised bed is the initial, successful collision between a droplet of granulating fluid and the powder particles. This is the fundamental growth module nucleus for the process and requires detailed consideration.

The process broadly described as collision can be subdivided into three specific sequences. These are classified as IMPACT, SPREADING and LIQUID BRIDGE FORMATION.

Impact

This term is used to describe the droplet and powder particles colliding. A number of factors influence this stage. The prime factor is the velocity of each component which is determined by the degree of atomisation for the droplet and the air flow rate of the fluidising air in the bed for the powder particles. Additional factors include size, shape and density of the components.

The initial impact results in the powder particles becoming partially covered by the droplet. The degree of liquid coverage is dependent upon the forces of collision and also on the volume of liquid. Spreading of the liquid then occurs.

Spreading of the liquid over the surface of the particles is a function of contact angle between the liquid and solid and surface tension, see e.g. Osterhof and Bartell (1930). The wettability of the powder by the liquid is therefore extremely important. This was shown in Chapter 5 when the hydrophobicity of a powder mix was related to granule size. The significance of spreading can perhaps be explained by considering more closely data of Chapter 5 and section 6.3.2 for salicylic acid and relating these results to surface changes. Addition of surfactant was shown to result in a significant increase in granule size of salicylic acid granules. This can be explained by a reduction in contact angle (increased cos θ) at the solid/liquid interface as the presence of surfactant was increased. The reduction in surface tension is also considered to exert an effect. As the liquid front advances a larger interfacial area is produced with the surfactant molecules migrating to the fresh air/ liquid and liquid/solid interfaces. It is suggested that the rate by which the liquid front advances is related to the concentration of surfactant molecules in the bulk solution. High surfactant concentrations promote spreading due to a concentration gradient effect. The extent and role of surfactant molecule adsorption at the solid/ liquid interface in hydrophobic systems may also be important. For high levels of surfactant increased adsorption may occur and result in a difference in surfactant molecule concentration between the two interfaces. It is possible that the improved spreading and adsorption at the solid/liquid interface may explain the large increases in granule size with high surfactant concentrations due to improved liquid/solid bond adhesion.

It is assumed that during spreading there is sufficient time for the migration of surfactant molecules to occur. Work by Ottewill (1972) has shown that the mean residence time of a molecule in a micelle is in the order of 10^{-4}s and the half life of a micelle following instantaneous dilution (an analogous situation to the generation of a larger interfacial area during atomisation (see section 5.6.4)) is 10^{-3}s. Thus the times are sufficiently rapid to allow these suggested migrations to occur.

Liquid Bridge Formation

The liquid spreads over the surface of the particles and completes entrapment. The degree by which the interstices between the particles are filled with liquid depends upon the size of droplet and also on the shape and size of the powder particles and to some extent on the bed environment i.e. the external factors such as fluidising air flow rate and temperature which influence evaporation. The factors which affect the tensile strength of the liquid bonds between the particles were described in Chapter 1 and will be discussed more fully in section 6.4.3 in relation to the model systems studied. It should however be noted that a monolayer of surfactant at the air/liquid interface reduces evaporation (section 5.6.4) and maintains the high level of liquid in the nuclei module.

Growth

After the initial collision and nuclei formation, growth occurs when more liquid is added to the bed. Size enlargement proceeds by either single particle addition or combination with another nuclei followed by reshaping. Change in shape is determined primarily by the fluidising air and thus tends towards a perfect sphere. These changes occur due to the liquid bridges being freely moveable. This area of growth is conventionally termed transition and is identified by a dramatic increase in growth rate. Changes in the sieve size fraction >180 <354 μm in Figs. 6.13a, 6.18 and 6.21 perhaps illustrate this point. The level of liquid in the bed is extremely important and is considered to be the rate determining influence upon growth. Growth continues in this manner until eventually a maximum size (Fig. 6.13b) is reached depending upon the values of the process variables (i.e. fluidising air temperature etc.). Subsequent growth is minimal and is due to abrasion transfer or layering. This latter growth area is normally in the conventional granulation ball growth region. However, depending upon the processing conditions in the bed, either overwetting occurs (at low evaporation rates) or the granules can be coated with binder solution (at high evaporation levels). It should be noted that the basic factors which influence initial formation of the nuclei module are common to the local changes occurring during single particle addition or nuclei/nuclei combination.

Solid Bridge Formation

Once liquid addition has been terminated and the wet mass dried the role of the binder becomes extremely important. As the water evaporates the level of liquid bridge is reduced and thereby the strength of the association between the powder particles. It is during this period that the adhesive qualities of the binder come into prominence. The binder concentration in the liquid increases during drying and passes through a transition stage before final solid bridge formation. It is during the transition stage that the 'quasi' binder bridges must be of sufficient strength to withstand the forces of disaggregation since they are a near rigid structure. Liquid bridges are readily moveable and therefore able to withstand these forces. Evidence suggests that some particles become dislodged during this stage as can be seen from Fig. 6.15d and identified by a crater of binder. It should be noted that during granulation, evaporation occurs and therefore the level of binder in the liquid bridges increases.

Distribution of binder in the dried granule was clearly shown by employing a solvent extraction method. The SEMs in Fig. 6.19 show a number of concentrated areas of binder with no evidence of significant solute migration of binder to the granule periphery. For hydrophobic particles the binder distribution becomes extremely important since the particles must be encapsulated within a matrix of binder for granule formation to occur. Areas of high binder concentration can be observed and these are attributed to either addition of a near dried droplet to the granule surface or to a nuclei module which has collided with a number of droplets during its formation and subsequently partially dried out and combined with another nuclei module.

The granule batches were processed under identical conditions (see section 6.3.1) and it is considered that the distribution of binder may change depending upon the values of the process variables i.e. an increase in evaporation levels during fluid addition will result in a smaller granule size but with a more concentrated binder matrix around the particles. In some systems this may be desirable to give improved granule compression properties.

Additional solid bridges are formed by crystallisation during drying. They are considered to be only supplementary to the solid

binder bridges since their effect upon total granule strength is considered not to be very significant. Fluidised bed granulation of lactose by water alone produces only limited size enlargement and is considered to support this point.

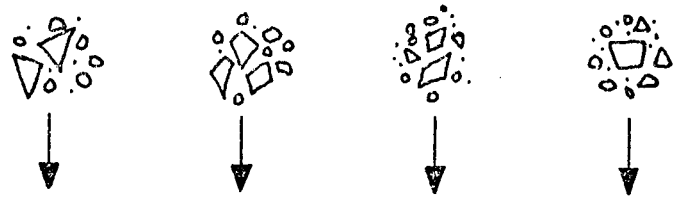
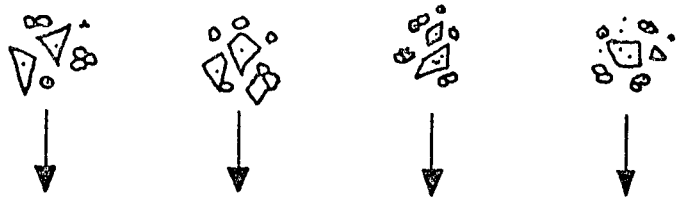
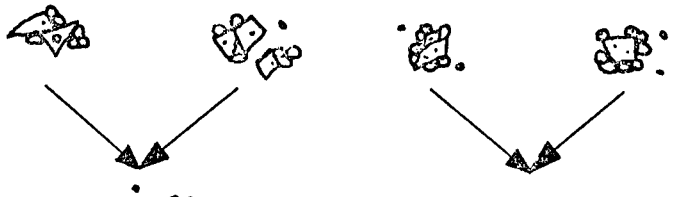
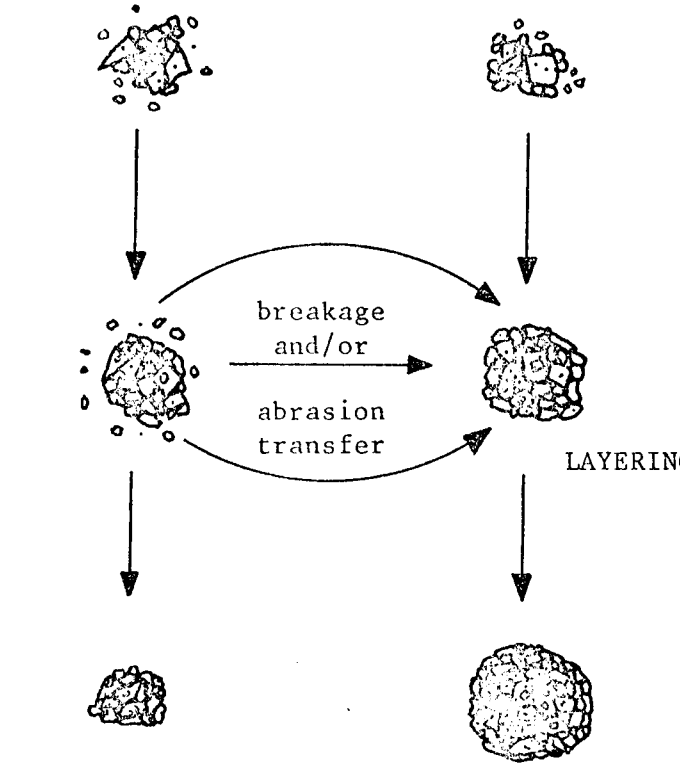
The presence of a surface layer of binder over the particles is perhaps an important area worth considering since a continuous covering has potential for dosage design of controlled release systems. It is suggested that the effect of Eudragit or ethylcellulose dissolved in the granulating solution may be worth investigating. The results from Chapter 5 in which surfactant was dissolved in the granulating solution perhaps support this concept. Improved granule flow was obtained presumably due to a possible glidant effect of sodium lauryl sulphate spread over the surface of the granules. The presence of surfactant in the PVP layer may also explain the differences in results of Chapter 5 between the mode of surfactant addition to the system. Larger granules are produced by sodium lauryl sulphate dissolved in the granulating solution and this is attributed to the localised effects, whilst, the dry surfactant mixed in the powder must dissolve before becoming active (see section 5.4.3). It is suggested that the surfactant may weaken the PVP solid bridges and thus when a diametral force is applied to a tablet, fracture occurs through the weakened PVP film. Tablets prepared from granules with surfactant added in the powder do not have such a continuous weakened film of PVP and thus can withstand a diametral force to a greater degree.

6.4.1 Lactose granulation

On examination of the particle size enlargement data in Figs. 6.9 and 6.10 and the evidence of the SEMs (Fig. 6.11), the following schematic diagram is suggested to explain the observed sequence of events (Fig. 6.24). The corresponding visual evidence from the SEMs is cross-referenced on this diagram.

During the early stages of fluid addition to the fluidised bed, combination between the primary lactose particles takes place. The combination occurs when a droplet collides and wets a particle. This particle then acts as a prime nucleus module and upon further collision with another particle (or particles) has sufficient liquid level to form a liquid bridge and thus successful adhesion. It is highly likely that particle/droplet/particle collisions occur. This early growth state is conventionally termed NUCLEATION (see section 1.2.3).

Fig. 6.24 MECHANISM OF FLUIDISED BED GRANULATION OF LACTOSE

TIME (min)	QUANTITY OF GRAN. FLUID ADDED (ml)	DIAGRAMMATIC REPRESENTATION OF MECHANISM	VISUAL EVIDENCE REF.
0	0		Fig. 6.11a
2	40		Fig. 6.11b
6	120		Fig. 6.11c & d
8	160		Fig. 6.11e
10	200		Fig. 6.11f & g

As more liquid is introduced into the system nucleation progresses steadily as the primary lactose particles combine. This is reflected in the gradual increase in the 90-180μm size fraction. The larger angular particles combine together between their flat surfaces; less liquid is required for a stronger degree of association.

After a period of 6 minutes (120 ml fluid addition) a sudden acceleration in growth occurs due to successful internuclei adhesion. This is caused by the nuclei reaching a high level of fluid content and therefore meeting the conditions necessary for optimum growth. Changes from pendular/funicular to capillary states of liquid content occur by a fresh droplet colliding with a nucleus. Sufficient excess fluid then becomes available to enable formation of liquid bridges between colliding nuclei. These bridges are of sufficient strength to withstand the forces of disaggregation within the bed caused by turbulence and attrition. Further growth also occurs by the remaining single particles adhering to the nuclei unit, particularly in the interstices between the larger crystals since only a small volume of liquid is necessary to secure successful adhesion. This stage is termed COALESCENCE. Growth continues in this region as additional fluid becomes available due to droplet collision with the larger nuclei unit. Eventually a near optimum size of granule is reached depending upon the values of the process parameters (Chapter 3); in this case after 8 to 9 minutes. This is identified by a plateauing region in the size versus time graph.

Subsequent size enlargement is much slower after this period and occurs by two methods: Breakage of large granules with the evolving fragments becoming distributed over the surfaces of the remaining granules; this is known as LAYERING. The second method, termed ABRASION TRANSFER is perhaps the more likely of the two. This occurs as the result of collision and abrasion of the formed granules when a small amount of material is transferred from one to the other in a truly random manner. This event causes only minimal changes in the total number of agglomerates.

At the higher levels of liquid content, lactose dissolves and thus solid crystalline bridges are also formed. The dissolved lactose may also significantly affect the tackiness of the liquid during drying and thus improve the adhesive qualities of the near dried PVP.

6.4.3 Modification of proposed Lactose mechanism by other ingredients.

In order to explain the differences in sieve fraction data shown in section 6.3.2 between the various excipients it is necessary to consider in more fundamental terms the factors influencing the tensile strength of liquid bridges. The tensile strength of a granule was shown by Rumpf (1958) to be approximately equal to the average capillary pressure ($\overline{P}$). An expression was derived showing that:

$$\overline{P} = \frac{\gamma}{M} \cos\theta$$

where $\cos\theta$ = solid/liquid contact angle

γ = surface tension

the term M is the hydraulic radius of the pores and can be approximated to:

$$M = \frac{\varepsilon}{S_v (1 - \varepsilon)}$$

ε = void fraction

S_v = specific surface of solids in the granule.

In a model system where particles are considered to be non-porous spheres $S_v = 6/d$ and a final expression is achieved:

(Eq. 6.1) $$\overline{P} = 6 \frac{(1 - \varepsilon)}{\varepsilon} \frac{\gamma}{d} \cos\theta$$ (d = particle diameter)

Newitt and Conway-Jones (1958) and Rumpf (1961) have confirmed the above equation by experimentation. This equation can be used to explain the factors influencing growth in the fluidised bed. The fundamental step to achieve granule formation in the fluidised bed is the successful collision between a droplet of granulating solution and a number of powder particles. During this collision the liquid bridges formed must be of sufficient strength to withstand the forces of disaggregation acting in the bed until liquid evaporates and solid binder bridges are formed. In the various systems studied the solid bridges of binder were formed by PVP. Provided the liquid bridges formed are sufficiently strong then growth proceeds rapidly as shown in Fig. 6.10 for lactose.

The physico-chemical properties of the various systems studied have a significant influence upon the tensile strength of the liquid bridges formed and thus to some extent modify the initial aggregation process and subsequent growth. By considering the various components used in the expression for tensile strength (Eq. 6.1) these modifications can be explained. Each component will be considered individually for clarity.

The contact angle, θ, was studied in Chapter 5 and shown to exert a significant effect upon granule size. For a hydrophobic system, where cos θ is low, the final strength of the liquid bridge after collision may be of insufficient magnitude to prevent disaggregation. This results in a slower rate of aggregation and subsequent growth, as was displayed by salicylic acid (Fig. 5.6). Theoretically improved growth can be obtained by reducing the contact angle thereby increasing cos θ. This indeed occurred on the addition of surfactant and can be readily observed from sieve fraction data (Fig. 6.18). Differences were also noted between the method of surfactant addition to the system i.e. whether dissolved in the granulating solution or added directly to the powder mix. During the early fluid additions growth was similar in both batches, although after 6 minutes fluid addition, a dramatic increase in particle size was exhibited by the batch with surfactant added directly to the powder mix. It is suggested that this change is due to the surfactant in the powder becoming activated i.e. dissolving to an extent whereby it was able to exert a number of effects upon the droplet/multiparticle combination. The prime effect is improved wettability which in turn promotes dissolution of the salicylic acid (which eventually form solid bridges of crystallisation) and improved spreading of liquid over the salicylic acid particles (aiding entrapment of the particles in a PVP envelope). The addition of surfactant is also considered to exert other more localised effects. The most important of these is on surface tension. This has a significant influence upon the final tensile strength value of the wet granule (page 242) as shown in Eq. 6.1. Recent work by Walker and Wells (1980) using various solvents has indicated that there is a direct relationship between surface tension and granule size in conventional wet granulation. This suggests that a low surface tension value due to surfactant may be expected to produce a

smaller granule size in the fluidised bed. However, this was not so in the present work since the addition of surfactant does not, however, solely affect surface tension. As previously shown in Chapter 5 the presence of surfactant also has a significant influence upon wettability resulting in an increase in cos θ. There are thus two mutually opposing effects upon tensile strength: the low surface tension value which reduces tensile strength and the increased cos θ value which improves tensile strength. The value of cos θ is increased by such magnitude due to the presence of surfactant that the reduction in value of surface tension is relatively small and there is therefore an increase in tensile strength and granule size (see Eq. 6.1, page 242). It is further considered that the high levels of surfactant in solution around the particles may result in localised boundary layers around the salicylic acid particles which exhibit a high degree of adhesiveness. The improved adhesiveness could exert a strong effect at the interparticulate points of contact. The presence of surfactant in liquids has been shown (Blokh et al, 1973; Kremnev et al, 1974) to reduce the rate of evaporation. In the fluidised bed the droplet/ multiparticle combination will be able to maintain a prolonged high level of liquid which aids successful collision and ultimately growth. Additional benefits from prolonged high liquid levels are improved salicylic acid dissolution with formation of bridges of crystallisation and an increase in the time period during which the salicylic acid boundary layer is in an adhesive state.

The value of the void fraction also significantly affects tensile strength. This is particularly evident from consideration of a two component system. For optimum tensile strength the void volume should be small. In conventional wet granulation the void volume is influenced by the mixing action of the paddle or impeller which forces the particles together and also the particle size and shape of the components in the formulation. In the fluidised bed the former effect is absent and thus the void fraction is primarily influenced by shape and size differences and distribution of the particles in the mix. This effect was shown by the starch/lactose and lactose/salicylic acid systems studied. SEM's of both systems (Figs. 6.14 and 6.23) clearly show the slightly smaller starch and salicylic acid particles in the interstices of the larger angular lactose crystals. During aggregation the reduced void fraction increases liquid bridge strength and thus improves growth. The influence of particle shape has not received sufficient attention with limited research published on this aspect. This could be

primarily attributed to the difficulties in sourcing large quantities of monosized particles with a well defined shape. However, it is considered that in this study the effect of shape has been to some extent qualitatively identified as shown by the behaviour of larger flat faced lactose crystals during granulation. Particle diameter also affects tensile strength due to void volume and this has been considered in respect to void volume for two component systems.

It is suggested that the momentum of particles and agglomerates (droplet/multiparticle combination) may exert an additional effect in the fluidised bed. Thus particle density may have a significant influence during the collision with another particle and finally result in a closer degree of association.

CONCLUSION

The growth mechanism and the structure of the final granule produced in the fluidised bed have been studied in a number of model systems using sieve fraction analysis, scanning electron microscopy and specially developed fluorescent techniques. Close examination of the data enabled a growth mechanism to be proposed for Lactose. Modifications to this mechanism for the other model systems have been discussed in detail. It was shown that the physico-chemical properties of the powder particles have a considerable effect upon the fundamental processes occurring during aggregation. By quantifying these properties it may be possible to more readily optimise formulations in the fluidised bed and thus control more closely granule quality.

CHAPTER 7.

OVERALL DISCUSSION AND CONSIDERATIONS FOR FUTURE WORK

7.1 OVERVIEW OF THE THESIS.

7.2 RELATIONSHIP OF THIS WORK TO FLUIDISED BED GRANULATION IN PRACTICE.

7.3 SUGGESTIONS FOR FUTURE WORK

CHAPTER 7

OVERALL DISCUSSION AND CONSIDERATIONS FOR FUTURE WORK

7.1 OVERVIEW OF THE THESIS

The initial work in this thesis, by necessity, investigated the effect of various process variables upon granule quality in view of the anomalous results cited in the literature. Those factors which exerted a significant effect upon granule quality were identified and quantified. More importantly, the overall conclusion indicated that the wetting of the powder in the bed had the most significant influence upon granule quality. This led to the work progressing in two directions a) characterising the mode of granulating solution addition together with the effect upon granulation and b) the effect of powder bed hydrophobicity and the influence of a surfactant .

The investigation into the sprays produced by atomisation showed that the size of droplets had a profound effect upon granule quality. A direct linear correlation was shown with larger droplets producing a coarser granule. Additional data also indicated that the droplet size distribution of the spray (Rosin-Rammler dispersion coefficient) and spray rate of granulating solution had significant effects. The importance of the role of the droplet was therefore established in the context of growth and this identified the need for a further in-depth study. It should be noted that during droplet size determination the use of the Malvern ST 1800 analyser was invaluable since readings were taken instantaneously in situ during atomisation. Thus errors normally associated with spray analysis using conventional entrapment techniques were eliminated. The data generated therefore gave a more accurate reflection of the actual spray characteristics of the atomised granulating solution than earlier workers in this field.

In Chapter 5 the significance of powder mix hydrophobicity was quantified. A linear correlation was shown between powder mix hydrophilicity ($\cos \theta$) and size of the granules produced. The addition of surfactant to a model hydrophobic system was shown to improve granulation. This was directly related to a reduction in powder/liquid contact angle. It was further shown that the addition of

surfactant dissolved in the granulating solution gave slightly coarse granules and better flow properties than those obtained by addition of surfactant powder directly to the mix. This was shown to be due to changes in spray characteristics of the atomised liquid and re-emphasised the importance of the role of the spray droplet on the process.

It was concluded from both of these investigations that growth and final granule structure required further attention. This was studied in Chapter 6, by initially employing a specially developed fluorescent technique followed by sieve fraction analysis data, an excipient extraction procedure and scanning electron microscopy. The changes occurring at various stages of liquid addition were followed. These were related to well-established conventional wet granulation mechanisms. A number of model systems were studied and a tentative growth mechanism proposed for lactose. Modifications to this mechanism for the other systems were discussed in detail and correlated to the differences in the physico-chemical properties of the various materials.

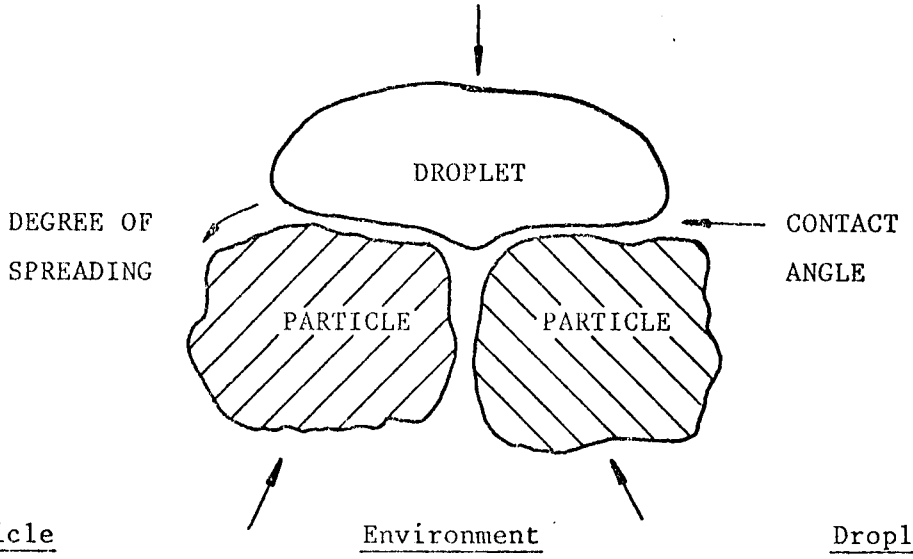
Results from Chapter 6 also demonstrated the need for closer examination of the powder particle/droplet combinations in terms of liquid level and the changes occurring in the microenvironment of the interfaces upon collision. Research into fluidised bed granulation has generally been directed towards the effect of process variables upon the system whilst perhaps not viewing the process from a more fundamental direction by considering the powder particle/droplet combinations and subsequently appraising localised changes occurring during adhesion.

The interrelationship between the results of these various studies can perhaps be best illustrated by considering the local changes and the series of events occurring during the collision between a droplet and two powder particles. A simple diagrammatic representation of the collision is shown in Fig. 7.1 together with those factors considered to be of importance for the successful formation of a nuclei module. This module is the basic building unit for granule growth in the fluidised bed and therefore ultimately determines granule quality.

The series of events occurring within the context of collision were classified as impact, spreading and liquid bridge formation and these have been discussed in section 6.4.1.

In conclusion, this work has examined many factors which affect the process of fluidised bed granulation. From these studies it was possible to isolate those factors which have a significant effect on granule quality. In general terms, these were found to be the physico-chemical properties of the starting materials and the properties of the droplets of granulating solution.

It is believed that further studies into these areas and also in the underlying mechanisms may help to eliminate many of the problems associated with fluidised bed granulation in practice by presenting a scientific basis for future product formulation and process optimisation. These studies will then lay the foundation for the true benefits of fluidised bed granulation to be realised.



Particle	Environment	Droplet
Size/Shape	Temperature	Size
Density	Air flow rate	Velocity
Porosity		Surface Tension
Hydrophobicity		Viscosity
Rugosity		
Velocity		

Fig. 7.1 Diagrammatic Representation of Droplet/Particle Collision Identifying Factors Influencing Successful Adhesion.

7.2 Relationship of this work to Fluidised Bed Granulation in practice

A large number of pharmaceutical companies in the late 1960's purchased FBGs as the "granulator of the 70s" anticipating that they would replace the conventional process.

Although the potential advantages of the FBG are, on paper, very encouraging, it was a different story when the pharmaceutical industry attempted to transfer their formulations from conventional apparatus to the fluidised bed. Wet granulation is a simple, robust technology whereas FBG is much more delicate. An empirical approach appears to work satisfactorily for wet massing, but not for fluidised bed granulation.

It is suggested that a lack of research into the fundamental underlying mechanisms of fluidised bed granulation could have significantly contributed to the troubles encountered by the industry and the subsequent demise of interest and application of the process. Since the first description of the apparatus and process by Wurster there has been only a relatively small quantity of work published on this topic, compared with, say, the more conventional granulation by wet massing.

Thus knowledge about fluidised bed granulation (which, because of its absence at the time, may have contributed to the pharmaceutical industry's initial lack of success with FBG) is now more freely available.

The quality of granules produced by fluidised bed granulation is the result of a complex interrelated balance between a number of factors. Small changes in the values of some of these factors can exert a tremendous influence upon granule quality. The process is therefore susceptible to minor variations in raw material characteristics which is perhaps one of the major reasons for its rather limited success in the pharmaceutical industry. Whilst accepting this to be a potential problem it is believed that excipient suppliers should aim for a tighter control on batch to batch raw material physical characteristics. Indeed this goal is becoming necessary for conventional processing in view of current attempts to eliminate tablet to tablet variability of dissolution and therefore bioavail-

ability. Once this has been achieved the FBG offers much closer control to produce granulations within tight size and size distribution limits.

For successful processing, formulators should characterise the physico-chemical properties of the raw material and consider in more fundamental terms the effects of excipient selection on granule quality. With this basis and the assumption that raw material variability can be eliminated it is possible to 'engineer' granulations with desired characteristics by only minor changes in the droplet size of the atomised granulating solution and liquid addition rate. This also results in the capability to closely control granule distribution of binder and additional dissolved components from the granulating solution. Not only does this offer improved granule compression and dissolution properties but also a tremendous potential for design and manufacture of various drug dosage systems.

The information from Chapter 3 is useful to the practice of FBG in the pharmaceutical industry since it identified and quantified the effect of a number of process variables upon granule quality i.e. a manufacturer can increase granule size by simply lowering air temperature and air flow rate, increasing granulating solution addition rate, reducing the degree of liquid atomisation and diluting the granulating solution. The usefulness of a torque arm mixer in analysis of granules was also shown. This method may provide a useful contribution to industry for rapid assessment of granule quality.

Data from Chapter 4 showed the importance of droplet size. Control of nozzle design and atomising air pressure is very important since this can be used to regulate droplet size and thereby granule quality. A rapid method for accurately determining spray droplet size was identified. This method may offer great benefits in other areas of pharmaceutical processing e.g. coating solution spray optimisation for tablet coating.

The study in Chapter 5 emphasised the previously little appreciated effect of raw material hydrophobicity upon processing. In addition, the chapter also showed a possible method of improving granulation by introducing a surfactant to the system.

As previously mentioned the lack of fundamental information was a problem. If the mechanisms are better understood then industry can apply this knowledge and therefore design a more efficient and predictable process. The results and theoretical considerations discussed in Chapter 6 have to some extent succeeded in achieving these aims and establishing a more fundamental appreciation of the process and approach to formulation.

It is probable that there will be a future for fluidised bed granulation. Admittedly it has proved very difficult, and in some cases impossible, to transfer existing formulations onto a fluidised bed, whereas this has been found to be relatively easy in most cases with high speed chopping granulators; the saving in time is very attractive.

However, FBG can be considered as a possible alternative for new formulations, particularly relatively low-dose hydrophilic formulae consisting of say, mainly lactose plus a small amount of starch. The saving in handling and total equipment costs must make it an alternative worth considering in these instances.

There are other specific occasions where FBG could be the method of choice. There are examples in the industry when the high shear in a conventional mixer/kneader produces granules which are either too hard or have too low a voidage (or both) which adversely affects their compression and dissolution characteristics. The absence of shear in a fluidised bed may provide the answer. The spherical granules that can be produced also have excellent flow properties.

Thus, in conclusion the transfer of traditional wet granulation to high speed choppers is very sensible with many existing formulations, however as we learn more from research about the process and mechanisms of fluidised bed granulation the possibility of its use should be seriously considered and not discarded without further thought, particularly for new formulations. However, it must be appreciated that FBG development requires time and effort.

7.3 SUGGESTIONS FOR FUTURE WORK

Many aspects of FBG have been discussed and investigated in this thesis. Various areas have been identified as being particularly important to the granulation process and the quality of the final granules. It is considered that some of these areas need further examination as do others not considered in this thesis. Suggestions for areas in which future work may be beneficial are listed below.

1. The physico-chemical properties of the starting materials are extremely important and it is considered that a study is necessary to relate their interrelationships to the basic wetting and aggregation area of growth. Once the effects have been quantified it may be possible to predict process performance of multicomponent systems and therefore final granule quality from a number of fundamental measurements.

2. Batch to batch variation in raw material has been identified as being a major problem in FBG. A comprehensive study is therefore suggested to clarify and quantify the effect of particle properties such as density, rugosity, porosity, size and size distribution upon the granulation process.

3. The inclusion of additional components dissolved with the binder in the granulating solution can have considerable advantages. This area requires investigation since the possible benefits include improved granule compression properties and thus tablet quality, improved dissolution and the use of controlled release coatings for dosage design.

4. It has been suggested that changes in liquid evaporation rates in the bed by increased fluidising air temperature and flow rate may result in changes in the deposition and distribution of binder. This may have a direct correlation with granule compression characteristics and thus on tablet quality. A detailed investigation into this area is therefore recommended. More extensive use of the solvent extraction technique together with scanning electron microscopy is considered necessary to achieve this aim.

5. The localised changes occurring at the solid/liquid interface with the possible formation of boundary layers exerting beneficial adhesive effects has been considered. Further examination of these changes is suggested.

6. The torque arm mixer gave extremely encouraging results and has great potential as a simple technique for quantifying granulations. Data has only been obtained from a lactose/starch formulation and it is suggested that a number of other formulations should be evaluated to more fully validate the technique.

BIBLIOGRAPHY

BIBLIOGRAPHY

Ahmad, M. and Pilpel, N. (1967) Mfg. Chem. and Aerosol News, 38(1), 137-138

Airth, J.M., Bray, D.F. and Radecka, C. (1967) J. Pharm. Sci., 56, 233

Andreev, B.V., Gorodnicher, V.I., Minina, S.A. and El-Banna, H.A. (1980) Pharm. Ind. 42 (12), 1304-1306

Arambulo, A.S., Suen Fu, H. and Deardorff, D.L. (1953) J. Am. Pharm. Ass. (Sci. Edn.) 42, 692

Azzopardi, B.J. and Yeoman, M.L. (1977), Unpublished Information, Leicester University

Bagster, D.F. and Bridgwater, J. (1967) Powd. Tech., 1, 189

Bank, A., Bezzegh, D. and Fekete, P. (1971) Proc. 2nd. Conf. Appl. Phys. Chem., 2, 687-92

Banks, M. (1974) Scherer Award Paper, unpublished in scientific journal.

Barlow, C.G. (1968) Chem. Eng. (London), No. 220, CE 196

Bellomo, N. (1974) Rarefied Gas Dyn., Proc. Int. Symp., 9, 2(F1)

Benarie, M.M. (1961) Brit. J. Appl. Phys., 12 (9), 514

Biedebach, F. (1960) Pharm. Ztg., 105, 1270

Bingham, E.C. and Wikoff, R.W. (1931) J. Rheol., 2, 395

Blokh, E.I., Neustroev, L.S., Sapiro, V.S. and Fainerman, V.N. (1973) Khim Tekhnol (Kiev), 2, 37-38

Borzunov, E.E. and Shevchenko, S.M. (1970) Farm. Zh. (Kiev), 25 (1), 60

Bradley, J.K. (1975) J. Appl. Chem. Biotechnol., 25, 891

British Pharmacopoeia (1980) Her Majesty's Stationary Office, London

British Standard, 410, 1976

British Standard, 1796, 1976

Brochmann-Hanssen, E. and Medina, J.C. (1963) J. Pharm. Sci., 52, 630

Brook, D.B. and Marshall, K. (1968) J. Pharm. Sci., 57, 481

Brown, R.L. and Richards, J.C. (1959) Trans. Am. Inst. Chem. Engrs., 37, 108

Brownley, C.A. and Lachman, L. (1964) J. Pharm. Sci., 53, 452

Bruil, H.G. and Van Aartsen, J.J. (1974) Colloid and Polymer Sci., 252, 32

Burlinson, H and Pickering, C. (1950) J. Pharm. Pharmac., 2, 630

Campy, D., Eaves, T., Grudzinski, E.M. and Worthington, H.E.C. (1974) J. Pharm. Pharmac., 26: Suppl. 76P

Capes, C.E. and Danckwerts, G.C. (1965) Trans. Instn. Chem. Engrs., 43, T116 and 125

Carli, F. and Simioni, L. (1977) Drug Dev. and Ind. Pharm., 3, 1

Carli, F. and Simioni, L. (1979) J. Pharm. Pharmac, 31, 128

Carstensen, J.T. (1973) "Theory of Pharmaceutical Systems Volume II/Heterogeneous Systems", Academic Press New York and London, Pages 186-191

Cassie, A.B.D. (1948) Disc., Farad. Soc., 3, 11

Chadwick, C.S., McEntegart, M.G. and Nairn, R.C. (1958) Immunology, 1, 315-327

Charlesworth, D.H. and Marshall, W.R. Jnr. (1960) A.I.Chem. E.J., 6 (1), 9

Chatfield, C. (1970) "Statistics for Technology", Penguin Books Ltd., London

Chodkowska-Granicka, B. (1968a) Farm. Pol., 24 (3), 211

Chodkowska-Granicka, B. (1968b) Farm. Pol., 25 (3), 299

Clare, H. and Radcliffe, A. (1954) J. Inst. Fuel, 27, 510

Cochran, W.G. and Cox, G.M. (1966) "Experimental Designs", 2nd Edition, Wiley & Sons, Inc., New York

Collett, J.H. and Kesteven, G. (1978) Drug Dev. and Ind. Pharm.,4(6), 555-584

Cook, D.T., Grant, D.J. and Newton, J.M. (1977), J. Pharm. Pharmac., 29: Suppl. 62P

Cooper, B.F. and Brecht, E.A. (1957) J. Amer. Pharm. Ass. (Sci. Edn.), 46, 520

Cooper, J., Swartz, C.J. and Suydam, W. Jnr. (1961) J. Pharm. Sci., 50, 67

Contini, S. and Atasoy, K. (1966) Pharm. Ind., 28, 144-146

Craik, D.J. (1958) J. Pharm. Pharmac., 10, 73

Craik, D.J. and Miller, B.F. (1958) J. Pharm. Pharmac., 10, 136T

Crooks, M.J. and Schade, H.W. (1978) Powd. Tech., 19, 103-108

Crosby, E.J. (1960) Am. Perfumer Arom., 75, 43

Csukás, B. and Ormós, Z. (1975) Int. Congr. Chem. Eng., Chem. Equip. Des. Autom., Proc. 5th, D, D4.22

Curlin, L.C. (1955) J. Amer. Pharm. Ass. (Sci. Edn.), 44, 16

Davies, W.L. and Gloor, W.T. (1971) J. Pharm. Sci., 60 (12), 1869 - 1874

Davies, W.L. and Gloor, W.T. (1972) J. Pharm Sci., 61 (4), 618-622

Davies, W.L. and Gloor, W.T. (1973) J. Pharm Sci., 62 (1), 170-172

Dingwall, D. and Ismail, S.I. (1977) J. Pharm. Pharmac., 29, 393-396

Dixon, K. (1959) J. Soc. Cosmet. Chemists, 10, 220-226

Dombrowski, N. and Tahir, M. (1977) J. Inst. Fuel, 50, 59

Dorman, R.G. (1952) Brit. J. Appl. Physics, 3, 189

Eisenklam, P. (1961) J. Inst. Fuel, 24, 130

Fainerman, V.B. and Sapiro, V.S. (1973) Kolloid Zh., 35(2), 392-394

Feigenbaum, L. (1969) Labo-Pharma-Problemes et Techniques, 177, 62-67

Frazer, R.P., Dombrowski, N. and Routley, J.B. (1963) Chem. Eng. Sci., 18, 339

Fraser, R.P. and Eisenklam, P. (1956) Trans. Instn. Chem. Engrs., 34, 294

French, W.N., Matsui, F., Cook, D. and Levi, L. (1967) J. Pharm. Sci., 56, 1622

Friedman, M. and Donbrow, M. (1978) Drug Dev. and Ind. Pharm., 4 (4), 319-331

Geist, J.M., York, J.L. and Brown, G.G. (1951) Ind. and Engng. Chem., 43, 1371-1373

Gold, G., Duvall, R.N., Palermo, B.T. and Slater, J.G. (1966a) J. Pharm. Sci., 55 (11), 1291

Gold, G., Duvall, R.N. and Palermo, B.T. (1966b) J. Pharm. Sci., 55 (10), 1133

Golitzine, N. (1951) National Aeronautical Establishment, Canada Note 6.

Goodhart, F.W., Draper, J.R. and Ninger, F.C. (1970) J. Pharm. Sci., 59, 540

Goodhart, F.W., Mayorga, G., Mills, M.N. and Ninger, F.C. (1968) J. Pharm. Sci., 57, 1770

Coulson, J.M. and Richardson, J.F. (1964) "Chemical Engineering", Pergamon Press Ltd., Oxford

Grey, R.O. and Beddow, J.K. (1968/69) Powd. Tech., 2, 323

Gunn-Smith, R.A. and Platt, N.E. (1961) Aerosol Age, Feb., 33-34

Gupte, A.V. (1973) Pharm. Ind., 35, 17-20

Gunsel, W.C. and Lachman, L. (1963) J. Pharm. Sci., 52, 178

Harada, K. (1972) Kagaku Kogaku, 36 (11), 1237-43

Harbert, F.C. (1974) Mfg. Chem. and Aerosol News, 45 (1), 23-25

Harwood, C.F. and Pilpel, N. (1968) Lab. Pract., 17 (11), 1236

Hasson, D. and Mizrahi, J. (1961) Trans. Instn. Chem. Engrs., 39, 415

Hausner, H.H. (1967) Int. J. Powder Met., 3 (4), 7

Hesketh, H.E. (1973) J. Air Pollut. Contr. Ass., 23 (7), 600

Hess, H. (1978) Pharm. Tech., 1(4), 37-106

Hicks, C.R. (1964) "Fundamental concepts in the design of experiments", Holt, Rinehart and Winston Inc., New York

Hurd, C.D. and Papas, A.G. (1959) J. Org. Chem., 24, 388

Iiyama, E. and Aoki, R. (1960) Chem. Eng. (Tokyo), 24, 205

Ingram, J.T. and Lowenthal, W (1966) J. Pharm. Sci., 55, 614

Johnson, R.E. and Dettre, R.H. (1966) "Surface and Colloid Science", Chapter on Wettability and Contact Angles, E. Matijevic (ed.), II

Johnson, M.C.R. (1979) J. Pharm. Pharmac., 31 (5), 273-276

Johnson, M.C.R., Rees, J.E. and Sendall, F (1975) J. Pharm. Pharmac., 27: Suppl. 80P

Jones, T.M. and Pilpel, N. (1966a) J. Pharm. Pharmac., 18, 429

Jones, T.M. and Pilpel, N. (1966b) J. Pharm. Pharmac., 18: Suppl. 182S

Jones, T.M. and Pilpel, N. (1966c) J. Pharm. Pharmac., 18, 81

Kala, H., Dittgen, M. and Moldenhauer, H (1971) Pharmazie, 26 (11), 664-675

Kapur, P.C. and Fuerstenau, D.W. (1966) Ind. Engng. Chem. (Proc. Des. and Dev.), 5, 5

Kassem, A.A. and Ghazy, F.S. (1974) J. Drug Res., 6 (3), 95

Kossen, N.W.F. and Heertjes, P.M. (1965) Chem. Eng. Sci., 20, 593

Kornblum, S.S. (1969) J. Pharm. Sci., 58 (1), 125-127

Kremnev, O.A., Dolinski, A.A. and Ivanitski, G.K. (1974) Dopov. Akad. Nauk, Ukr. RSR, SER A, 36 (10), 932-4

Kulling, W. (1976) "Measures and Installations for Making Fluid Bed Dryers and Fluid Bed Spray Granulators Safe Against Dust and Solvent Explosions", company manuscript, Aeromatic AG, March

Kulling, W. and Simon, E.J. (1980) Pharm. Tech., 3 (1), 29-33

Kuno, H. and Senna, M. (1967) Rheol. Acta., 6 (3), 284

Kuno, H. and Kurihara, K. (1965) Rheol. Acta., 4, 73

Langmuir, I. and Blodgett, K.B. (1946) AAF Technical Report 5418, Army Air Forces, Air Material Command, Dayton, Ohio

Lazarus, J., Pagliery, M. and Lachman, L. (1964) J. Pharm. Sci., 53, 798

Lehrman, G.P. and Skauen, D.M. (1958) Drug Stand., 26, 170

Lerk, C.F., Schoonen, A.J.M. and Fell, J.T. (1976) J. Pharm. Sci., 65 (6), 843

Leva, M. (1959) "Fluidisation", McGraw-Hill Book Company, New York

Levy, G., Antkowiak, J.M., Procknal, J.A. and White, D.C. (1963) J. Pharm. Sci., 52, 1047

Levy, G. and Gumtow, R.H. (1963) J. Pharm. Sci., 52 (12), 1139

Liske, T. and Mobus, W. (1968) Drugs made in Germany, 11 (4), 182-189

Marks, A.M. and Sciarra, J.J. (1968) J. Pharm. Sci., 57, 497

Marshall, W.R. Jnr. (1954) Chem. Engng. Progress Mono. Ser., 50 (2), 3

Matsumoto, S. and Takashima, Y. (1971) J. Chem. Eng. (Japan), 4 (3), 257-263

McGreath, C.G. and Beer, J.M. (1976) Applied Energy, 2, 3

McKee, I.K. and Herbst, W. (1962) U.S. Pat. 3,034,911

Mehta, A., Adams, K. and Zoglio, M.A. (1977) J. Pharm. Sci., 66 (10), 1462-1464

Motto, D. (1977) Boll. Chim. Farm., 116, 307-313

Mugele, R.A. and Evans, H.D. (1951) Ind. and Engng. Chem., 43, 1319-1324

Nairn, R.C. (1969) "Fluorescent Protein Tracing", 3rd Edition, E. and S. Livingstone Ltd., Edinburgh and London

Negus, C. and Azzopardi, B.J. (1978), Dept. Physics Report, University Leicester

Nelson, E., Long, S. and Wagner, J.G. (1964) J. Pharm. Sci., 53, 1224

Newitt, D.M. and Conway-Jones, J.M. (1958) Trans. Instn. Chem. Engrs., 36, 422

Neumann, B.S. (1953) "Flow properties in disperse systems", (Hermanns, J.J., ed.). Chapter 10, North Holland Publishing Co., Amsterdam

Newton, R.H., Dunham, G.S. and Simpson, T.P. (1945) Trans. Am. Inst. Chem. Engrs., 41, 215

Novosad, J. and Standart, G. (1965) Collection Czechoslov. Chem. Commun., 30, 3247

Nukiyama, S. and Tanasawa, Y. (1938) Trans. Soc. Mech. Engrs. (Japan), 4 (14), 86

Nukiyama, S. and Tanasawa, Y. (1939) Trans. Soc. Mech. Engrs. (Japan), 5 (15), 138

Ormós, Z. (1973) Hung. J. Ind. Chem., 1, 207-228

Ormós, Z., Pataki, K. and Csukás, B. (1973a) Hung. J. Ind. Chem., 1, 307-328

Ormós, Z., Pataki, K. and Csukás, B. (1973b) Hung. J. Ind. Chem., 1, 463-474

Ormós, Z., Pataki, K. and Csukás, B. (1973c) Hung. J. Ind. Chem., 1, 475-492

Ormós, Z., Pataki, K. and Csukás, B. (1975a) Hung. J. Ind. Chem., 3, 193-216

Ormós, Z., Pataki, K. and Csukás, B. (1975b) Hung. J. Ind. Chem., 3, 631-646

Osterhof, H.J. and Bartell, F.E.J. (1930) Phys. Chem., 34, 1399

Ottewill, R.H., Post Grad. School on Theory and Practice of Solubilisation, Apr. 1972, Univ. of London

Otvos, L., Marton, J. and Agoston, J.M. (1960) Tetrahedron Lett., p15

Padday, J.F. (1951) "Proceedings of the Second International Congress on Surface Activity", Vol. 3, Butterworths, London, England, pp 81-121

Parfitt, G.D. (1969) "Dispersion of Powders in Liquids", Elsevier, Amsterdam, The Netherlands

Pearse, A.G.E. (1968) "Histochemistry - Theoretical and Applied", 3rd Edition, London: Churchill

Peck, W.C. (1939) Pharm. J., 141, 27 and 57

"Perry's Chemical Engineer's Handbook" (1973) 5th Edition, McGraw-Hill, Tokyo, p 8-57

Pharmaceutical Codex (1979) The Pharmaceutical Press, London

Pietsch, W. (1965) Diss. T.H. Karlsruhe

Pietsch, W and Rumpf, H. (1966) Report to the International Convention of CNRS Paris 18th - 20th April

Pilpel, N. (1964) J. Pharm. Pharmac., 16, 705

Pilpel, N. (1965) Chem. Process Engng., 46, 167

Priestley, R.J. (1962) Chem. Eng., July, 125-132

Prioux, P., Lefort Des Ylouses, D., Seiller, M. and Duchene, D. (1975) J. Pharm. Belg., 30 (2), 132-146

Quinn, M.F. (1963) Ind. and Engng. Chem., 55, 18

Raff, A.M., Arambulo, A.S., Perkins, A.F. and Deardorff, D.L. (1955) J. Am. Pharm. Ass. (Sci. Edn.), 44, 290

Raff, A.M., Robinson, M.J. and Svedres, E.V. (1961) J. Pharm. Sci., 50 (1), 76-78

Rankell, A.S., Scott, M.W., Lieberman, H.A., Chow, F.S. and Battista, J.V. (1964) J. Pharm. Sci., 53 (3), 320

Richards. J.H. (1972) in "Tutorial Pharmacy", Chapter 4, Pages 37-38, 6th Edition, Pitman Medical, London

Ridgway, K. and Rubinstein, M.H. (1971) J. Pharm. Pharmac., 23: Suppl. 11S-17S

Ridgway, K. and Segovia, E. (1966) Mfg. Chem. and Aerosol News, 36(12), 39-44

Riggs, J.L., Seiwald, R.J., Burckhalter, J.H., Downs, C.M. and Metcalf, T.G. (1958) Amer. J. Path., 34, 1081-1097

Riley, G.S. and Mann, G.R. (1972) Mat. Res. Bull., 7, 163

Rinderknecht, H. (1962) Nature, 193, 167-168

Ritschel, W.A. (1971) Pharm. Ind., 33 (10), 685-9

Ritschel, W.A. and Erni, W. (1977) J. Pharm. Sci., 66 (10), 1438-1441

Rosin, P. and Rammler, E. (1933) J. Inst. Fuel, 7, 29

Rouiller, M., Gurny, R. and Doelker, E. (1975) Act. Pharm. Technol., 21 (2), 129-138

Rubinstein, M.H. and Ridgway, K (1974) J. Pharm. Pharmac., 26:Suppl. 24P-29P.

Rue, R. (1976) Private Communication, School of Mechanical Engineering, Leicester Polytechnic, Leicester

Rumpf, H. (1958) Chem. Ing. Tech., 30, 144 and 329

Rumpf, H. (1961) Int. Symp. Philadelphia, Pa., and (1962) in "Agglomeration" (Edited by Knepper, W.A.) Interscience, New York, Pages 379-418

Ryder, J. (1979) Int. J. Pharm. Tech. and Prod. Mfr. (1979) 1 (1), 14-25

Sastry, K.V.S. and Fuerstenau, D.W. (1973) Powd. Tech., 7, 97-105

Schaefer, T. and Wørts, O. (1977a) Arch. Pharm. Chem. Sci. Ed., 5, 51-60

Schaefer, T. and Wørts, O. (1977b) Arch. Pharm. Chem. Sci. Ed., 5, 178-193

Schaefer, T. and Wørts, O. (1978a) Arch. Pharm. Chem. Sci. Ed., 6, 1-13

Schaefer, T. and Wørts, O. (1978b) Arch. Pharm. Chem. Sci. Ed., 6, 14-25

Schaefer, T. and Wørts, O. (1978c) Arch. Pharm. Chem. Sci. Ed., 6, 69-82

Scott, M.W. Lieberman, H.A., Rankell, A.S., Chow, F.S. and Johnston, G.W. (1963) J. Pharm. Sci., 52, 284-291

Scott, M.W., Lieberman, H.A., Rankell, A.S. and Battista, J.V. (1964) J. Pharm. Sci., 53 (3), 314

Seager, H. (1977) Mfg. Chem. and Aerosol News, 48 (4), 25-35

Seager, H., Burt, I., Ryder, J., Rue, P., Murray, S., Beal, N. and Warrack, J.K. (1979) Int. J. Pharm. Tech. and Prod. Mfr., 1 (1), 36-44

Seager, H and Taskis, C.B. (1976) Mfg. Chem. and Aerosol News, 47 (12), 27

Shafer, E.G.E., Wollish, E.G.and Engel, C.E. (1956) J. Am. Pharm. Ass. (Sci. Edn.), 45, 114

Shinoda, A., Nasu, T., Furikawa, M., Sakashita, S., Uesugi, K., Miyake, Y. and Toyoshima, S. (1976) Yakuzaigaku, 36 (2), 83-88

Simon, E.J. (1978) Mfg. Chem. and Aerosol News, 49(1), 23-32

Singiser, R.E. and Lowenthal, W. (1961) J. Pharm. Sci., 50 (2), 168-170

Sittig, M. (1953) Chem. Eng., May, 219-231

Smith, A.N., (1949a) Pharm. J., 182, 194

Smith, A.N., (1949b) Pharm. J., 182, 227

Spitael, J. and Kinget, R. (1977) Acta. Pharm. Technol., 23 (4), 267-277

Swithenbank, J., Beer, J.M., Taylor, D.S., Abbott, D. and McCreath, G.C. (1976) Univ. Sheffield Dept. Chem. Eng. and Fuel Technol. Report HIC 245

Taneya, S. (1963) Japan J. Appl. Phys., 2, 728

Taneya, S. (1965) Japan J. Appl. Phys., 4 (4), 297

Thurn, U. (1970) Dissertation No. 4511, Eidgenossischen Technischen, Hochschule, Zurich

Travers, D.N., Rogerson, A.G. and Jones, T.M. (1975) J. Pharm. Pharmac., 27: Suppl.

Tuerck, P.A., Walters, E.L. and Carkhuff, E.D. (1960a) J. Amer. Pharm. Ass. (Sci. Edn.), 49, 344

Tuerck, P.A., Walters, E.L. and Carkhuff, E.D. (1960b) J. Amer. Pharm. Ass. (Sci. Edn.), 49, 347

Vanacek, V., Markvart, M. and Drbohlav, R. (1966) "Fluidised Bed Drying", Leonard-Hill, London, England, p.31

Wagner, J.G. (1961) J. Pharm. Sci., 50, 359

Walker, C.V. and Wells, J.I. (1980) Proc. 2nd Brit. Pharm. Tech. Conf., Solid Dosage Research Unit, Liverpool

Ward, J.B. and Trachtenberg, A. (1962) Drug Cosmet. Ind., 91, 35

Washburn, E.D. (1921) Phys. Rev., 17, 374

Webster, A.R. and Van Abbé, N.J. (1955) J. Pharm. Pharmac., 7, 882

Weighardt, K. (1952) Ing. Arch., 20, 109

Wolf, G. (1968) Drugs Made in Germany, 11, 172-180

Wolff, J.E., Dekay, H.G. and Jenkins, G.L. (1947) J. Am. Pharm. Ass. (Sci. Edn.), 36, 407

Wørts, O. (1972) Pharm. Int., 6, 12-15

Wurster, D.E. (1959) J. Am. Pharm. Ass. (Sci. Edn.), 48 (8), 451-454

Wurster, D.E. (1960) J. Am. Pharm. Ass. (Sci. Edn.), 49, 82

Yates, F. (1937) "The Design and Analysis of Factorial Experiments", Imp. Bur. Soil Sci. Tech. Comm. 35. (ex National Lending Library)

APPENDICES

Appendix I — Relationship between Refractive Index and PVP Concentration.

Appendix II — Calibration curve for absorbance of salicylic acid in artificial gastric juice at a wavelength of 300 nm against concentration.

Appendix III — Results of granule tests carried out on each run.

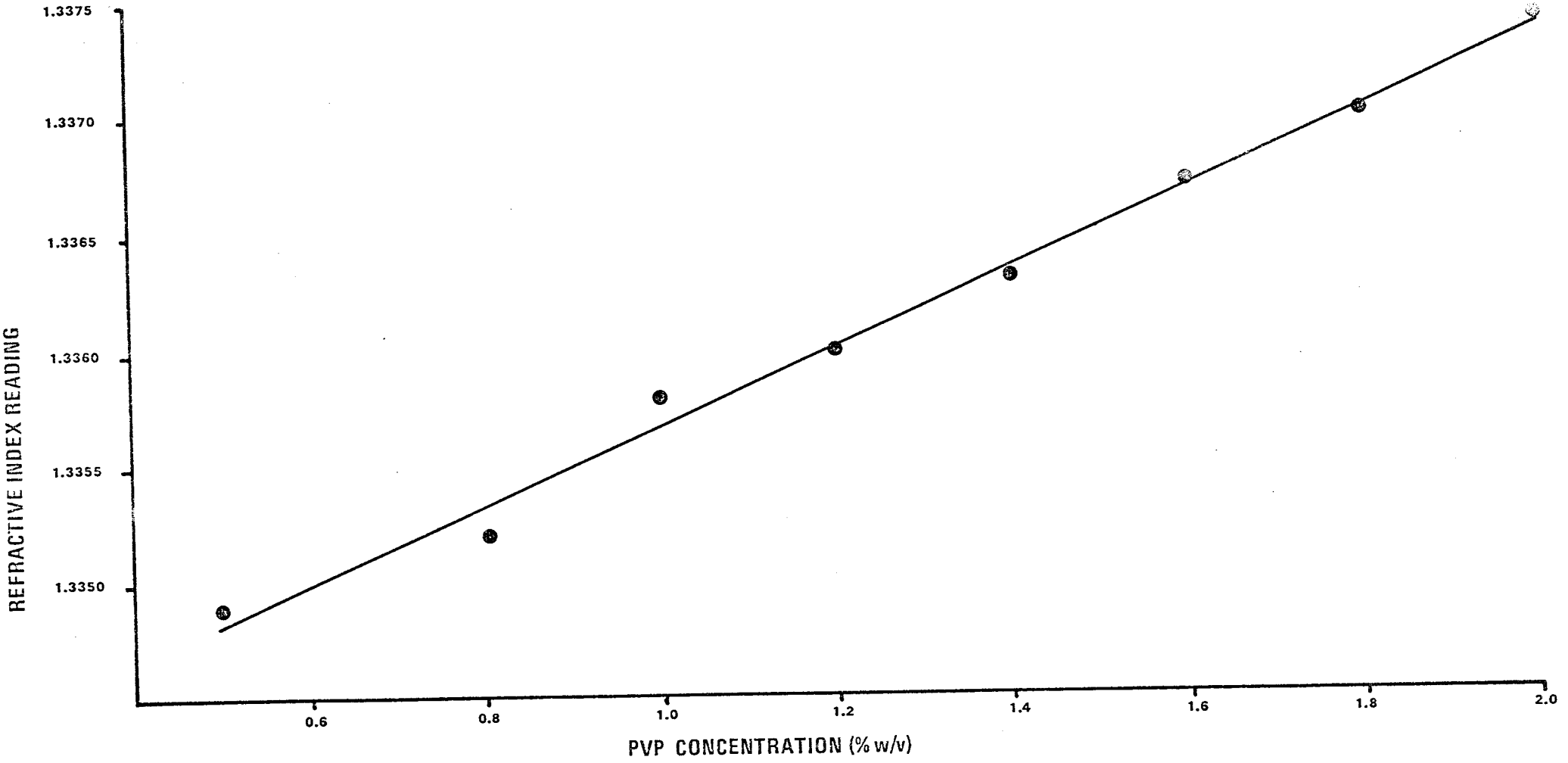
Appendix IV — Typical computer print out for Yates' Analysis.

Appendix V — Torque values measured for each granule batch produced from the experiment of 2^7 Factorial design.

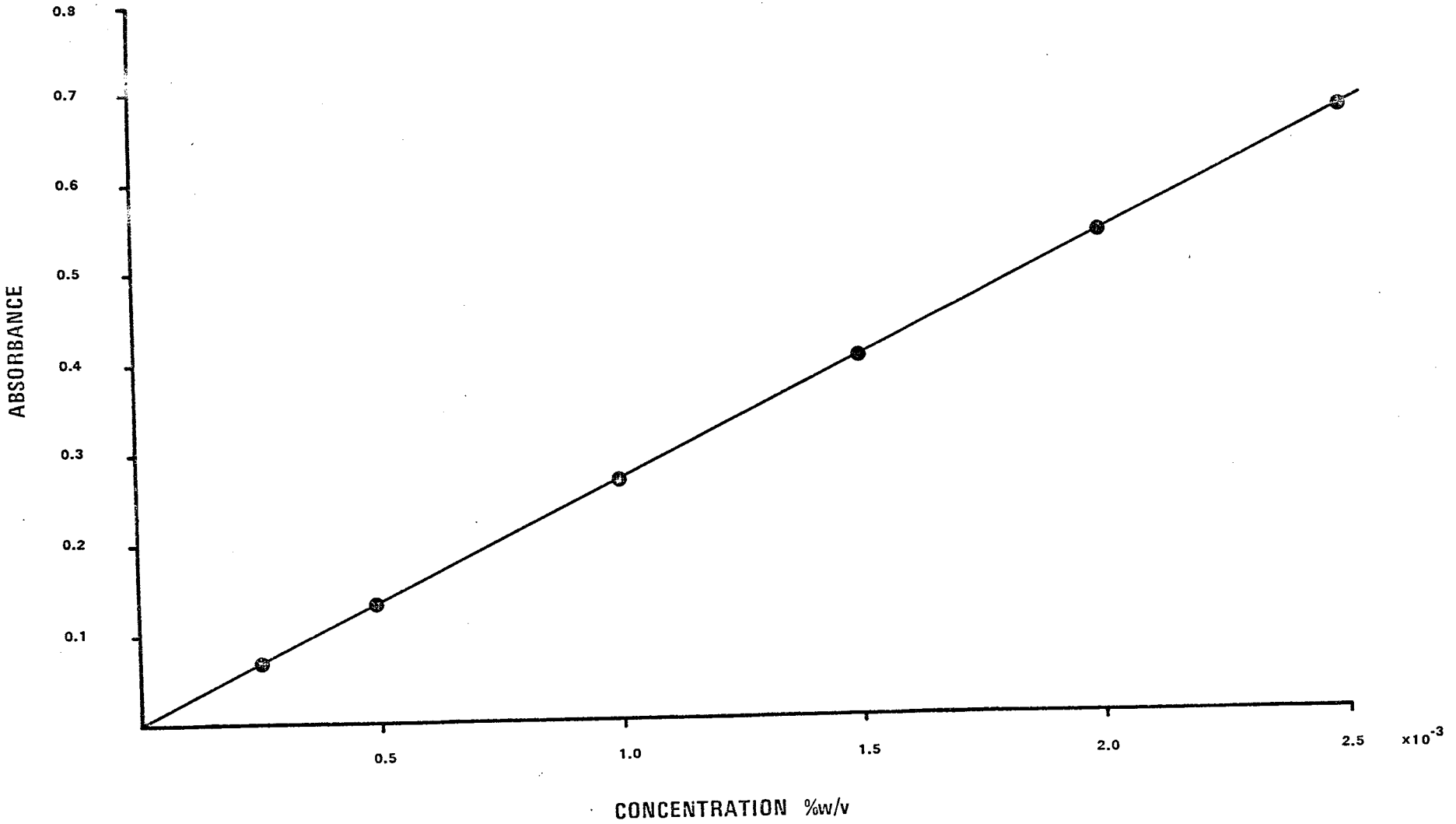
Appendix VI — Table of spray characteristics with rank order values for each of the eight granule batches prepared from a specific spray variable combination.

Appendix VII — Calculations to derive the area available per sodium lauryl sulphate molecule at the surface of atomised solutions.

Appendix VIII — Published Work in Fluidised Bed Granulation Technology and related fields in which M. Banks was involved during the course of this study.



Appendix I. Relationship between Refractive Index and PVP Concentration



Appendix II. Calibration curve for absorbance of salicylic acid in artificial gastric juice measured at a wavelength of 300 nm against concentration

APPENDIX III

Results of granule tests carried out on each run

Run No.	Variable Format ref. Table 3.5 (1 2 3 4 5 6 7)	FLOW THROUGH ORIFICE: 12mm Circular ($g\ s^{-1}$)	FLOW THROUGH ORIFICE: Smallest sized orifice: Orifice Diam. (mm)	FLOW THROUGH ORIFICE: Smallest sized orifice: Flow Rate ($g\ s^{-1}$)	Angle of Repose (°)	BULK VOLUME PARAMETER: Volume(ml) occupied by 50g material: No. of taps: 0	20	100	250	500	Poured bulk density (ρ_p) $g\ ml^{-1}$	Tap bulk density (ρ_t) $g\ ml^{-1}$	Hausner Ratio ρ_t/ρ_p	Mean Particle size (μm)
1	- - - - - - -	11.45	4.00	0.657	51.65	98.0	84.0	82.0	80.5	80.0	0.510	0.625	1.2255	152.75
2	- - - - - - +	10.10	6.35	2.155	52.50	92.0	76.5	74.0	73.0	72.0	0.544	0.694	1.2757	160.00
3	- - - - - - - +	11.17	4.00	0.565	51.00	104.5	88.5	86.5	84.5	83.0	0.478	0.602	1.2594	147.25
4	- - - - - - + +	0.00	0.00	0.000	59.05	95.0	77.0	75.0	72.5	72.0	0.526	0.694	1.3194	145.50
5	- - - + - - +	9.97	4.00	0.502	53.65	106.5	90.0	88.0	86.0	85.0	0.469	0.588	1.2537	152.00
6	- - - + - + +	0.00	0.00	0.000	60.40	92.5	75.5	72.5	70.5	68.5	0.540	0.730	1.3519	144.25
7	- - - + - + -	0.00	0.00	0.000	56.20	93.0	76.0	73.5	72.0	71.0	0.538	0.704	1.3086	146.25
8	- - - + - - -	11.03	4.00	0.613	52.25	98.0	84.0	81.5	80.0	79.0	0.510	0.633	1.2412	141.00
9	+ - - + - - +	0.00	0.00	0.000	61.60	94.0	76.5	73.0	71.0	70.0	0.532	0.715	1.3440	142.75
10	+ - - + - + +	0.00	0.00	0.000	-	86.0	70.5	67.0	65.5	64.0	0.581	0.781	1.3442	141.75
11	+ - - + - - -	0.00	0.00	0.000	56.10	106.0	87.5	84.0	82.5	81.0	0.472	0.617	1.3072	144.00
12	+ - - + - + -	0.00	0.00	0.000	60.65	95.0	75.0	71.0	70.0	68.5	0.526	0.730	1.3878	137.00
13	+ - - - - - -	7.58	7.14	2.368	54.15	101.5	85.5	83.0	81.0	79.5	0.493	0.629	1.2759	140.75
14	+ - - - - + -	0.00	0.00	0.000	60.20	85.0	72.0	69.0	67.0	66.0	0.588	0.758	1.2891	154.00
15	+ - - - - - +	0.00	0.00	0.000	61.40	108.0	90.0	86.5	85.0	83.5	0.463	0.599	1.2937	145.25
16	+ - - - - + +	0.00	0.00	0.000	-	90.0	73.0	71.0	69.0	67.5	0.556	0.741	1.3327	155.00
17	+ + - - - - -	12.53	4.00	0.597	52.45	95.5	81.5	78.5	77.5	76.5	0.524	0.654	1.2481	137.25
18	+ + - - - + -	10.38	4.00	0.598	52.45	95.0	81.0	79.0	78.0	76.5	0.526	0.654	1.2433	155.00
19	+ + - - - - +	10.00	4.00	0.520	52.85	101.0	85.0	82.0	80.5	80.0	0.495	0.630	1.2727	150.25
20	+ + - - - + +	8.72	7.14	2.417	53.10	98.0	85.0	81.0	79.0	78.0	0.510	0.641	1.2569	161.00
21	+ + - + - - +	10.20	4.00	0.563	52.30	103.5	87.0	84.5	82.5	81.5	0.483	0.613	1.2692	130.00
22	+ + - + - + +	8.27	4.75	1.010	53.35	97.5	83.0	80.0	78.0	77.0	0.513	0.649	1.2651	156.00
23	+ + - + - - -	9.97	4.00	0.572	52.30	100.0	85.0	82.0	80.0	79.5	0.500	0.629	1.2580	144.00
24	+ + - + - + -	10.58	3.20	0.385	52.35	96.0	82.0	79.0	78.0	77.5	0.521	0.645	1.2380	136.00
25	- + - + - - -	13.00	4.75	1.210	50.25	97.5	83.5	80.5	79.0	78.5	0.515	0.637	1.2417	151.25
26	- + - + - + -	15.03	4.00	0.615	50.25	89.0	76.5	74.5	74.0	73.0	0.562	0.685	1.2189	180.00
27	- + - + - - +	13.72	4.75	1.010	49.75	97.0	85.0	82.0	80.5	79.5	0.515	0.629	1.2214	147.00
28	- + - + - + +	12.05	4.00	0.605	56.65	92.5	79.0	77.0	75.5	74.5	0.540	0.671	1.2426	159.75
29	- + - - - - +	11.37	4.00	0.583	53.10	97.5	82.5	79.5	78.5	78.0	0.513	0.641	1.2495	156.50
30	- + - - - + +	14.18	4.00	0.587	50.75	92.5	80.5	78.0	77.0	76.5	0.540	0.654	1.2111	160.50
31	- + - - - - -	14.25	4.75	1.102	49.40	94.5	82.5	79.0	78.5	77.0	0.529	0.649	1.2268	148.50
32	- + - - - + -	14.27	4.00	0.580	49.70	90.5	79.0	76.0	75.0	73.5	0.552	0.680	1.2319	164.50

APPENDIX III cont'd

Run No.	Variable Format ref.Table 3.5 1 2 3 4 5 6 7	FLOW THROUGH ORIFICE 12mm Circular ($g\ s^{-1}$)	Smallest sized orifice Orifice Diam. (mm)	Flow Rate ($g\ s^{-1}$)	Angle of Repose (°)	BULK VOLUME PARAMETER Volume(ml)occupied by 50g material No. of taps 0	20	100	250	500	Poured bulk density (ρ_p) $g\ ml^{-1}$	Tap bulk density (ρ_t) $g\ ml^{-1}$	Hausner Ratio ρ_t/ρ_p	Mean Particle size (μm)
33	- + - - + - +	14.38	4.00	0.618	53.00	99.0	86.0	83.5	82.0	80.5	0.505	0.621	1.2297	154.00
34	- + - - + + +	13.70	3.20	0.368	50.45	93.0	83.0	81.0	79.0	78.5	0.538	0.637	1.1840	165.00
35	- + - - + - -	13.85	4.00	0.640	51.70	97.0	84.5	81.5	80.5	79.0	0.515	0.633	1.2291	162.00
36	- + - - + + -	16.30	4.00	0.635	44.70	89.5	78.5	77.0	75.5	74.5	0.559	0.671	1.2004	210.00
37	- + - + + - +	14.50	4.00	0.598	49.95	98.0	85.5	84.0	82.5	81.5	0.510	0.613	1.2020	151.00
38	- + - + + + +	13.57	4.00	0.525	51.40	97.0	84.5	82.5	80.5	79.5	0.515	0.629	1.2214	154.00
39	- + - + + - -	14.45	4.00	0.593	50.00	96.5	84.0	82.0	80.5	80.0	0.518	0.625	1.3264	151.50
40	- + - + + + -	15.48	4.00	0.560	49.30	91.5	81.5	80.0	78.5	78.0	0.546	0.641	1.1740	187.00
41	+ + - + + - +	10.45	3.20	0.398	52.60	106.5	91.0	88.0	86.0	85.0	0.469	0.588	1.2537	136.00
42	+ + - + + + +	8.95	4.75	0.952	52.45	102.0	85.0	82.5	81.0	79.5	0.490	0.629	1.2837	135.50
43	+ + - + + - -	10.43	4.00	0.637	53.00	102.0	88.0	85.0	83.0	82.0	0.490	0.610	1.2449	125.00
44	+ + - + + + -	11.08	4.00	0.580	52.15	100.5	85.0	82.5	81.5	80.5	0.497	0.621	1.2495	140.75
45	+ + - - + - +	9.80	3.20	0.408	51.60	103.0	88.0	86.0	83.5	83.0	0.485	0.602	1.2412	136.00
46	+ + - - + + +	10.53	4.00	0.340	52.10	100.0	85.0	82.0	80.5	79.5	0.500	0.629	1.2580	145.00
47	+ + - - + - -	9.78	4.00	0.527	51.50	103.0	88.5	85.5	84.0	83.0	0.485	0.602	1.2412	139.00
48	+ + - - + + -	9.78	4.00	0.527	51.20	100.0	85.0	82.0	80.0	79.5	0.500	0.629	1.2580	152.00
49	+ - - - + - +	0.00	0.00	0.000	54.90	110.5	90.5	87.5	85.5	84.0	0.452	0.595	1.3164	139.00
50	+ - - - + + +	0.00	0.00	0.000	-	89.0	72.0	69.0	67.5	66.5	0.562	0.752	1.3381	107.00
51	+ - - - + - -	6.60	7.14	0.407	53.80	106.5	88.5	86.5	85.0	83.5	0.469	0.599	1.2772	137.00
52	+ - - - + + -	0.00	0.00	0.000	-	95.0	77.0	74.0	72.5	72.0	0.526	0.694	1.3194	114.00
53	+ - - + + - +	0.00	0.00	0.000	-	102.0	83.0	79.0	77.0	76.0	0.490	0.658	1.3429	131.00
54	+ - - + + + +	0.00	0.00	0.000	-	93.0	75.0	72.0	70.0	68.5	0.538	0.730	1.3569	121.00
55	+ - - + + - -	7.17	3.20	0.332	52.60	109.0	92.0	89.0	88.0	87.0	0.459	0.575	1.2527	137.00
56	+ - - + + + -	0.00	0.00	0.000	61.20	100.0	80.0	77.5	75.0	74.0	0.500	0.676	1.3520	135.50
57	- - - + + - +	8.53	4.75	0.915	52.80	116.0	95.0	93.0	92.0	91.0	0.431	0.550	1.2761	146.25
58	- - - + + + +	0.00	0.00	0.000	59.90	101.0	83.0	80.0	77.5	76.5	0.495	0.654	1.3212	146.50
59	- - - + + - -	9.70	6.35	0.238	53.60	104.0	88.0	86.0	84.0	83.5	0.481	0.599	1.2453	140.00
60	- - - + + + -	11.18	4.00	0.570	54.70	96.5	82.0	80.0	78.5	77.0	0.518	0.649	1.2529	148.50
61	- - - - + - -	11.63	4.00	0.615	52.70	99.0	86.0	84.0	83.0	82.0	0.505	0.610	1.2079	150.00
62	- - - - + + -	8.83	4.75	1.058	53.00	96.0	82.0	79.0	77.5	77.0	0.521	0.649	1.2457	152.00
63	- - - - + - +	7.30	7.14	0.602	55.35	111.0	93.0	89.5	87.5	86.5	0.450	0.578	1.2844	162.00
64	- - - - + + +	0.00	0.00	0.000	-	100.5	80.0	77.0	74.0	72.5	0.497	0.690	1.3883	147.00

APPENDIX III cont'd

Run No.	Variable Format ref. Table 3.5 1 2 3 4 5 6 7	FLOW THROUGH ORIFICE: 12mm Circular ($g\ s^{-1}$)	FLOW THROUGH ORIFICE: Smallest sized orifice: Orifice Diam. (mm)	FLOW THROUGH ORIFICE: Smallest sized orifice: Flow Rate ($g\ s^{-1}$)	Angle of Repose (°)	BULK VOLUME PARAMETER: Volume(ml) occupied by 50g material: No. of taps: 0	20	100	250	500	Poured bulk density (ρ_p) $g\ ml^{-1}$	Tap bulk density (ρ_t) $g\ ml^{-1}$	Hausner Ratio ρ_t/ρ_p	Mean Particle size (μm)
65	- - + - + - -	13.40	4.00	0.592	52.35	98.5	85.5	84.0	82.5	81.5	0.508	0.613	1.2067	146.50
66	- - + - + + -	10.38	4.00	0.655	53.35	93.0	79.0	77.0	76.0	75.0	0.538	0.667	1.2398	161.75
67	- - + - + - +	11.00	4.00	0.515	54.05	105.5	90.0	88.0	86.0	85.0	0.474	0.588	1.2405	128.00
68	- - + - + + +	6.95	10.30	1.612	56.60	103.0	86.5	83.0	81.0	80.0	0.485	0.625	1.2887	137.50
69	- - + + + - -	11.95	4.00	0.637	56.60	101.0	86.5	85.0	83.5	82.0	0.495	0.610	1.2323	139.50
70	- - + + + + -	10.42	4.75	1.117	55.10	96.0	81.5	79.5	78.5	78.0	0.521	0.641	1.2303	135.00
71	- - + + + - +	7.08	6.35	1.877	53.80	107.0	90.0	87.5	86.0	85.0	0.467	0.588	1.2591	127.00
72	- - + + + + +	0.00	0.00	0.000	57.45	102.5	83.5	80.0	78.0	76.5	0.488	0.654	1.3402	145.00
73	+ - + + + - +	7.02	4.75	0.955	54.40	115.5	98.0	94.0	92.5	91.0	0.433	0.549	1.2679	139.00
74	+ - + + + + +	0.00	0.00	0.000	-	98.5	83.0	79.5	77.0	75.5	0.508	0.662	1.3031	128.75
75	+ - + + + - -	7.42	4.00	0.768	53.40	106.5	90.0	88.0	87.0	86.0	0.469	0.581	1.2388	120.00
76	+ - + + + + -	0.00	0.00	0.000	55.40	99.5	80.5	79.0	77.5	76.0	0.502	0.658	1.3108	142.25
77	+ - + - + - -	7.40	3.20	0.375	54.40	109.0	91.0	89.0	88.0	87.0	0.459	0.575	1.2527	127.00
78	+ - + - + + -	6.27	11.90	6.267	56.00	100.0	83.5	80.0	78.0	77.0	0.500	0.649	1.2980	134.00
79	+ - + - + - +	5.70	11.90	5.700	56.40	117.0	93.0	91.5	90.0	89.0	0.427	0.562	1.3162	142.00
80	+ - + - + + +	0.00	0.00	0.000	-	95.0	79.0	76.5	74.5	73.0	0.526	0.685	1.3023	126.00
81	+ + + - + - +	10.95	4.00	0.605	52.85	100.5	85.0	83.5	81.5	80.0	0.497	0.625	1.2575	136.00
82	+ + + - + + +	8.58	4.00	0.497	53.50	98.5	84.0	80.5	79.5	78.0	0.508	0.641	1.2618	142.50
83	+ + + - + - -	10.68	4.00	0.567	51.95	101.0	85.0	83.0	81.5	80.5	0.495	0.621	1.2545	127.00
84	+ + + - + + -	9.85	3.20	0.388	52.75	97.0	84.0	81.5	79.5	78.5	0.515	0.637	1.2369	135.00
85	+ + + + + - +	9.80	4.00	0.743	52.35	101.0	86.0	84.0	82.0	81.0	0.495	0.617	1.2465	125.00
86	+ + + + + + +	9.95	3.20	0.390	52.10	97.0	83.0	80.5	79.0	79.0	0.515	0.633	1.2291	133.00
87	+ + + + + - -	11.00	4.00	0.565	52.85	101.5	86.0	83.0	82.0	81.0	0.493	0.617	1.2515	129.00
88	+ + + + + + -	10.62	4.00	0.573	52.30	99.0	85.0	83.0	81.5	80.5	0.505	0.621	1.2297	135.00
89	- + + + + - -	12.68	4.00	0.590	47.95	94.0	83.0	80.0	78.5	78.0	0.532	0.641	1.2049	156.50
90	- + + + + + -	14.00	4.00	0.582	50.30	89.0	79.0	76.5	75.0	74.5	0.562	0.671	1.1940	166.00
91	- + + + + - +	11.75	4.00	0.560	51.30	95.0	82.5	79.5	78.5	77.5	0.526	0.645	1.2262	153.00
92	- + + + + + +	14.17	4.00	0.603	52.20	92.0	80.0	77.5	76.0	75.5	0.544	0.662	1.2169	156.00
93	- + + - + - -	12.97	4.75	1.102	50.45	92.0	81.0	79.0	77.5	77.0	0.544	0.649	1.1930	156.00
94	- + + - + + -	12.62	4.00	0.527	53.00	88.5	75.0	73.5	72.0	71.0	0.565	0.704	1.2460	177.00
95	- + + - + - +	9.85	5.60	1.152	53.25	90.0	75.0	73.5	73.0	72.5	0.556	0.690	1.2410	118.00
96	- + + - + + +	11.50	4.00	0.572	52.30	94.5	80.0	77.5	77.0	75.5	0.529	0.662	1.2514	166.00

APPENDIX III cont'd

Run No.	Variable Format ref. Table 3.5 1 2 3 4 5 6 7	FLOW THROUGH ORIFICE: 12mm Circular ($g\ s^{-1}$)	FLOW THROUGH ORIFICE: Smallest sized orifice: Orifice Diam. (mm)	FLOW THROUGH ORIFICE: Smallest sized orifice: Flow Rate ($g\ s^{-1}$)	Angle of Repose (°)	BULK VOLUME PARAMETER: Volume(ml) occupied by 50g material: No. of taps: 0	20	100	250	500	Poured bulk density (ρ_p) $g\ ml^{-1}$	Tap bulk density (ρ_t) $g\ ml^{-1}$	Hausner Ratio ρ_t/ρ_p	Mean Particle size (μm)
97	- + + - - - -	13.23	4.75	1.118	46.35	87.0	76.0	73.5	73.0	72.0	0.575	0.694	1.2070	165.50
98	- + + - - + -	14.13	4.00	0.595	49.35	90.0	80.0	78.0	76.5	75.0	0.556	0.667	1.1996	188.00
99	- + + - - - +	10.67	4.00	0.517	49.55	92.0	80.0	77.5	76.0	75.0	0.544	0.667	1.2261	156.00
100	- + + - - + +	13.88	4.00	0.623	51.95	91.0	79.0	76.0	75.0	74.0	0.550	0.676	1.2291	166.00
101	- + + + - - -	14.73	4.00	0.513	51.35	91.0	81.0	78.5	77.0	76.0	0.550	0.658	1.1964	172.00
102	- + + + - + -	13.80	4.75	0.642	49.50	87.5	77.0	75.0	74.0	73.0	0.571	0.685	1.1996	169.00
103	- + + + - - +	10.78	4.75	1.083	53.35	93.0	80.0	78.0	76.5	75.5	0.538	0.662	1.2305	168.00
104	- + + + - + +	14.28	4.00	0.603	50.40	90.0	78.0	76.0	75.0	74.5	0.556	0.671	1.2068	160.00
105	+ + + + - - -	9.97	4.00	0.597	50.90	100.0	84.5	82.5	80.5	80.0	0.500	0.625	1.2500	124.00
106	+ + + + - + -	10.35	4.00	0.555	51.65	97.5	82.0	80.0	79.0	78.5	0.513	0.637	1.2417	128.00
107	+ + + + - - +	10.73	4.00	0.807	53.65	101.0	85.0	82.5	81.0	80.5	0.495	0.621	1.2545	149.00
108	+ + + + - + +	8.80	4.00	0.548	51.80	101.0	85.0	82.0	80.5	79.5	0.495	0.629	1.2707	127.00
109	+ + + - - - -	10.18	3.20	0.423	53.25	100.5	85.0	83.0	81.5	81.0	0.497	0.617	1.2414	127.00
110	+ + + - - + -	10.00	4.00	0.573	52.30	98.5	85.0	82.0	80.5	80.0	0.508	0.625	1.2303	137.00
111	+ + + - - - +	9.90	4.00	0.558	52.40	101.0	86.0	82.5	81.5	80.5	0.495	0.621	1.2545	138.00
112	+ + + - - + +	9.97	4.00	0.537	51.20	98.0	84.0	82.0	80.0	79.0	0.510	0.633	1.2412	133.00
113	+ - + - - - -	8.35	4.00	0.557	52.10	103.0	89.0	87.0	85.5	85.0	0.485	0.588	1.2124	127.00
114	+ - + - - + -	7.80	6.35	4.052	52.75	97.5	83.0	80.0	78.5	77.0	0.513	0.649	1.2651	139.00
115	+ - + - - - +	9.05	4.00	0.522	53.90	105.5	91.0	87.0	86.0	85.0	0.474	0.588	1.2405	122.00
116	+ - + - - + +	6.52	11.90	6.517	55.60	102.0	83.0	80.0	79.0	78.0	0.490	0.641	1.3082	142.00
117	+ - + + - - -	9.33	4.00	0.462	53.00	103.5	87.0	85.0	83.5	83.0	0.483	0.602	1.2464	133.00
118	+ - + + - + -	8.42	10.30	5.752	53.95	97.0	83.0	80.0	78.5	77.5	0.515	0.645	1.2524	136.00
119	+ - + + - - +	7.65	3.20	0.350	54.05	107.0	91.5	88.0	87.0	86.0	0.467	0.581	1.2441	127.00
120	+ - + + - + +	5.05	11.90	5.050	-	101.0	84.0	80.0	78.0	76.0	0.495	0.658	1.3293	144.00
121	- - + - - - -	13.30	4.00	0.605	51.50	98.0	85.0	84.0	82.0	81.0	0.510	0.617	1.2098	154.00
122	- - + - - + -	8.70	4.75	0.755	55.50	94.0	78.0	76.0	74.0	73.0	0.532	0.685	1.2876	153.00
123	- - + - - - +	10.88	4.00	0.552	52.70	101.5	86.0	84.0	82.5	82.0	0.493	0.610	1.2373	156.00
124	- - + - - + +	8.62	4.75	0.948	55.00	94.0	81.5	79.0	77.5	76.5	0.532	0.654	1.2293	151.00
125	- - + + - - +	10.73	4.00	0.573	52.45	102.0	88.0	86.0	84.0	83.0	0.490	0.602	1.2286	130.00
126	- - + + - + +	8.07	6.35	1.865	53.40	99.0	83.0	80.0	79.0	78.0	0.505	0.641	1.2693	144.00
127	- - + + - - -	11.62	4.00	0.523	52.60	101.5	87.0	85.5	83.5	82.5	0.493	0.606	1.2292	149.00
128	- - + + - + -	10.53	4.00	0.545	52.20	94.0	80.0	77.5	76.5	75.5	0.532	0.662	1.2444	156.00

Run No.	Mean Particle Size	I	II	III	IV	V	VI	Effect Total VII	Effect	Sum of Squares
1	152.750	291.500	579.250	1152.750	2111.000	4553.000	9394.250	19675.000	23.7031	**********
2	140.750	285.750	573.500	1154.250	2743.000	4641.250	9312.750	-1375.000	-10.5469	2761.132813
3	144.500	281.000	540.250	1148.500	2317.000	4564.500	-491.750	523.500	9.3438	2761.173828
4	137.250	292.500	573.000	1144.500	2223.250	6446.250	-883.250	1007.500	-6.3672	1297.314453
5	154.000	285.000	580.000	1171.250	2438.750	-319.000	144.250	1243.500	-0.3398	627.904297
6	127.000	295.250	566.500	1145.750	2425.750	-161.750	450.250	-125.500	-2.0078	129.031451
7	145.500	282.000	593.500	1115.000	2390.500	-483.500	-146.750	-42.000	-0.5625	11.781250
8	127.000	296.000	545.000	1134.250	2256.750	-249.750	-269.750	1159.000	-2.4443	197.507813
9	141.000	287.000	599.250	1250.500	-157.000	77.000	-180.250	-234.500	-3.6641	424.611328
10	144.000	301.000	572.000	1184.250	-161.750	67.250	-123.250	54.500	0.8438	24.939453
11	151.250	273.500	571.750	1235.750	-104.500	256.000	-84.250	-24.000	-0.3750	4.500000
12	144.000	281.000	574.000	1190.000	-555.250	194.250	-40.250	-189.000	-2.9531	279.070313
13	148.000	277.000	591.000	1214.000	-194.750	-104.000	121.750	97.000	1.5156	73.507813
14	133.000	276.500	593.000	1176.500	-248.750	-42.750	-163.750	23.000	0.3594	4.132813
15	172.000	259.500	544.250	1134.000	-71.500	-202.000	-47.250	91.500	1.4297	65.408203
16	124.000	285.500	584.000	1119.750	-178.250	-54.750	-72.750	-309.500	-4.8359	744.361328
17	150.000	292.500	613.500	-84.750	23.000	-48.000	-72.750	-111.500	-1.7422	97.126953
18	137.000	306.750	617.000	-65.250	89.000	-112.250	-161.750	-111.500	-1.7422	97.126953
19	142.000	274.000	589.250	-84.500	72.500	-80.500	3.250	129.000	2.0156	130.007813
20	139.000	284.000	589.000	-76.500	-5.250	-42.750	53.250	49.000	0.7656	18.757813
21	146.500	294.750	620.000	-60.250	76.250	-132.000	83.250	-51.000	-0.7969	20.320313
22	127.000	277.000	607.750	-44.250	179.750	47.750	-107.250	826.000	12.9063	1417.781250
23	156.000	257.000	611.750	-9.000	56.000	8.500	-127.750	154.500	2.4140	186.486328
24	127.000	317.000	578.250	-46.250	135.250	-48.750	-61.250	18.500	0.2891	2.673828
25	140.000	301.000	622.000	-80.500	-53.000	45.000	107.750	5.000	0.0781	0.195313
26	137.000	290.000	592.000	-114.250	-51.000	76.750	-5.750	74.000	1.1562	42.781250
27	151.500	270.000	601.500	-165.750	-12.000	-100.000	-33.250	-91.500	-1.4297	65.408203
28	125.000	254.000	575.000	-83.000	-30.750	-63.750	56.250	22.500	0.3516	3.955078
29	134.500	277.250	564.000	-32.000	-96.250	-18.000	94.750	11.500	0.1797	1.033203
30	120.000	287.000	592.000	-39.500	-105.750	-29.250	-7.250	-172.500	-2.6953	232.470703
31	156.500	264.000	587.000	-95.000	-67.000	-19.000	-62.250	113.000	1.7656	99.757813
32	129.000	278.000	582.750	-83.250	8.250	-92.750	37.750	-9.000	-0.1406	0.632813
33	147.250	314.000	-23.250	3.750	-8.000	-40.500	-161.750	-232.000	-3.6250	420.500000
34	145.250	319.500	-65.500	28.250	-40.000	-32.250	-147.750	345.000	5.3906	926.125000
35	158.500	292.000	-4.250	23.500	-25.000	-108.000	49.250	-71.500	-1.1172	39.939453
36	150.250	325.000	-44.000	25.500	-87.250	-53.750	-180.750	204.500	3.1953	326.720703
37	136.000	283.250	-36.000	30.250	-26.750	29.500	-56.750	-26.500	-0.4141	5.486328
38	122.000	315.000	-48.500	42.250	-53.750	-25.250	185.750	125.500	1.9766	125.017578
39	156.000	292.000	-39.500	-27.000	-56.500	69.000	-16.750	68.000	1.0625	36.125000
40	138.000	297.000	-47.000	21.750	13.750	4.250	65.750	-85.000	-1.3281	56.445313
41	148.000	266.000	-8.250	38.500	-102.000	22.500	-94.250	62.500	0.9766	30.517578
42	142.750	362.000	-52.000	37.750	-33.000	60.750	51.250	-98.500	-1.5391	75.798828
43	147.000	295.750	-26.250	112.250	-38.500	-45.500	198.750	22.000	0.3438	3.781250
44	130.000	317.000	-22.000	87.250	-61.750	227.250	3.000	0.046875	0.070313	
45	130.000	284.000	-41.000	27.000	-57.750	-43.500	-83.250	58.000	0.9063	26.281250
46	127.000	327.750	12.000	29.000	61.750	-84.250	-71.250	-34.000	-0.5313	9.031250
47	148.000	277.250	-30.250	101.000	-78.500	-52.500	-3.250	51.500	0.8047	20.720703
48	149.000	301.000	-16.000	37.250	29.750	-4.750	21.750	-108.500	-1.6953	91.970703
49	162.000	300.500	-15.500	-10.750	23.000	26.500	-32.750	-147.500	-2.3047	169.970703
50	139.000	321.500	-65.000	-42.250	22.000	79.250	37.750	4.500	0.0703	0.158203
51	154.000	293.000	-53.250	-19.500	79.500	-7.000	-61.750	-120.000	-1.8750	112.500000
52	136.000	299.000	-61.000	-31.500	-2.750	1.250	135.750	64.000	1.0000	32.000000
53	128.000	285.750	-98.000	11.750	-0.250	-22.500	18.250	67.000	1.0469	35.070313
54	142.000	315.750	-69.750	-23.750	99.750	-10.750	-109.750	44.000	0.6875	15.125000
55	118.000	288.000	-59.250	9.000	-68.000	51.000	8.250	46.500	0.7266	16.892578
56	136.000	287.000	-23.750	-19.750	-17.750	5.250	-28.750	-122.500	-1.9141	117.216328
57	146.250	254.000	10.000	-40.500	-34.000	15.500	36.750	75.000	1.1719	43.945313
58	131.000	310.000	-42.000	-55.750	16.000	83.250	-25.750	-134.000	-2.0938	140.281250
59	151.000	263.500	-6.500	-38.250	12.000	8.500	-94.250	33.500	0.5234	8.765578
60	136.000	308.500	-33.000	-71.500	-41.250	-11.250	-28.250	-17.500	-0.2734	2.392578
61	127.000	267.500	-60.000	-33.000	-19.750	5.500	-22.250	11.500	0.1797	1.033203
62	139.000	289.500	-35.000	-34.000	0.750	-67.750	135.250	-137.500	-2.1484	147.158203
63	153.000	273.750	-48.000	8.000	-47.000	36.500	13.750	-210.000	-3.2813	344.531250
64	125.000	289.000	-39.250	0.250	-45.750	1.250	-22.750	59.000	0.9219	26.281250
65	140.000	-12.000	-7.750	-5.250	5.500	-66.500	-11.750	815.500	12.7422	1355.251953
66	154.000	-11.250	11.500	-2.250	-66.000	-96.750	-134.250	-211.500	-3.3047	389.470703
67	144.500	-27.000	10.250	-31.500	-25.500	-11.000	154.250	304.000	4.7500	721.531250
68	155.000	-34.500	14.000	-4.500	-4.750	-138.750	193.750	-114.000	-1.7813	101.531250
69	153.000	1.000	14.000	-27.250	-62.250	-4.000	-9.750	37.000	0.5781	10.695313
70	139.000	-7.250	9.500	2.250	-45.750	53.250	-61.750	41.000	0.6250	12.500000
71	148.000	-16.000	23.750	14.250	-63.750	-54.000	61.250	-285.500	-4.4609	636.781250
72	137.000	-44.000	26.000	-29.250	-14.250	-106.750	143.250	-64.500	-1.0078	32.501953
73	146.250	-13.000	14.250	-16.500	20.500	21.000	-68.250	-89.000	-1.3906	47.882813
74	137.000	-23.000	16.000	-10.250	8.500	-77.750	17.750	453.500	7.0859	1597.531250
75	180.000	-19.500	-17.750	-20.250	12.000	103.500	179.750	-190.500	-2.9766	283.517578
76	136.000	-29.000	40.000	-33.500	-37.250	82.250	-53.250	66.500	1.0391	34.516602
77	156.000	-1.000	-11.000	-30.000	-33.750	2.000	31.750	-108.500	-1.6953	91.970703
78	136.000	-24.500	-16.000	-28.500	82.750	-14.750	36.250	89.500	1.3984	62.590078
79	169.000	-19.500	9.750	4.000	-7.500	-9.500	-11.250	-104.000	-1.6250	67.781250
80	124.000	-27.500	12.000	5.750	11.750	75.250	-73.750	100.000	1.5625	78.125000
81	152.000	-2.000	5.500	-42.250	20.500	-12.000	8.250	14.000	0.2188	1.531250
82	114.000	-6.250	33.000	-59.750	2.000	-62.250	54.250	-210.000	-3.2813	344.531250
83	210.000	-14.000	32.750	-12.500	12.000	-27.000	-53.750	282.500	4.4141	621.781250
84	152.000	-18.000	5.000	-17.500	44.750	70.250	-44.750	82.500	1.2891	21.128828
85	141.750	-9.250	98.000	-43.750	-0.750	72.000	38.250	137.500	2.1484	147.705078
86	134.000	-17.000	16.250	0.250	-44.750	126.750	-16.250	28.500	0.4453	6.345703
87	177.000	-3.000	43.750	73.000	2.000	119.000	-40.750	12.000	0.1875	1.125000
88	135.000	-19.000	23.750	14.250	-63.750	108.250	43.750	25.000	0.3906	4.882813
89	148.500	-23.000	21.000	-49.500	-31.500	-1.000	49.750	70.500	1.1016	38.830078
90	135.500	-18.000	6.000	-7.750	-12.000	-82.250	8.250	197.500	3.0859	304.736328
91	187.000	14.000	39.000	24.250	-35.500	-99.500	11.750	-128.000	-2.0000	128.000000
92	140.750	18.000	-1.000	35.500	-48.750	29.250	-45.750	-35.000	-0.5469	9.570313
93	139.000	-15.250	36.000	-52.000	-15.250	50.000	67.750	-62.000	-0.9688	30.031250
94	142.250	-15.000	45.000	-24.500	-17.250	-53.250	-16.250	16.000	0.2500	2.000000
95	166.000	12.000	22.000	25.000	-1.000	23.500	-73.250	157.500	2.4609	193.798828
96	135.000	-28.000	15.250	4.750	-7.750	1.250	-35.250	-34.500	-0.5391	10.408203
97	145.500	-4.000	0.750	19.250	3.500	-51.500	-25.750	-204.500	-3.1953	326.720703
98	155.000	-9.500	11.500	3.750	23.000	18.750	-121.750	39.500	0.6172	12.189453
99	140.500	-14.000	10.250	-4.500	29.500	14.500	57.250	-52.000	-0.8125	21.125000
100	161.000	-51.000	-32.000	26.500	46.750	21.250	-52.750	82.000	1.2812	52.531250
101	191.000	-9.250	-10.000	1.750	6.250	-12.500	-98.750	102.000	1.5938	81.281250
102	142.000	-44.000	-9.500	27.750	13.250	-49.250	-21.250	-233.000	-3.6406	424.132813
103	166.000	-20.000	-23.500	-5.000	3.500	116.500	-20.750	4.500	0.0703	0.158203
104	153.000	-41.000	-8.000	2.250	-2.250	19.250	84.750	-62.500	-0.9766	30.517578
105	144.250	-36.000	-4.250	27.500	-17.500	-18.500	-30.250	46.000	0.7188	16.531250
106	141.500	-58.000	16.000	-27.750	-5.000	38.750	97.250	9.000	0.1406	0.632813
107	159.750	-27.750	-7.750	-79.750	48.000	-44.000	54.750	-54.500	-0.8516	23.205078
108	156.000	-42.000	-16.000	-20.000	-68.750	-65.750	-10.750	84.500	1.3203	55.783203
109	144.000	-13.000	5.000	-15.000	41.750	19.500	-81.250	-41.500	-0.6484	13.455078
110	144.000	-46.250	4.000	-31.000	9.250	-13.250	127.750	-57.500	-0.8984	25.812500
111	160.000	7.250	0.250	-11.000	25.500	-22.000	-103.250	-44.000	-1.3125	55.125000
112	127.000	-31.000	-40.000	-4.750	-20.250	-4.750	-19.250	35.000	0.5469	11.281250
113	167.000	9.500	-3.500	-12.250	-15.500	19.500	17.250	-94.000	-1.4688	72.000000
114	107.000	0.500	+37.000	-21.750	31.000	17.250	4.750	-110.000	-1.7188	94.531250
115	165.000	-9.000	-34.750	0.500	18.000	-19.500	-36.750	77.500	1.2109	46.921828
116	145.000	-33.000	-21.000	15.500	7.250	-5.750	-97.250	105.500	1.6484	86.955078
117	137.500	-2.750	+20.000	20.250	-55.750	17.500	55.250	127.500	1.9922	127.001953
118	124.000	-3.750	-14.250	-4.250	59.750	-106.750	-21.750	-65.500	-1.0234	33.517578
119	166.000	0.000	+13.250	-1.000	-16.000	-17.500	-32.750	209.000	3.2656	341.257813
120	142.500	-33.000	-18.250	-40.250	4.250	-43.750	15.250	84.000	1.3125	55.125000
121	144.500	-40.000	-2.000	-33.500	-9.500	46.500	+2.250	-65.500	-1.0234	33.517578
122	121.000	-20.000	-24.000	13.750	15.000	-97.750	13.750	-60.500	-0.9453	28.595703
123	154.000	-11.500	-1.000	5.750	-28.500	115.000	-110.250	-77.000	-1.2031	46.320313
124	135.500	-23.500	-33.000	-5.000	-39.250	23.250	-13.750	48.000	0.7500	18.000000
125	145.000	-25.500	20.000	-15.000	47.250	24.500	-115.250	16.000	0.2500	2.000000
126	128.750	-18.500	-12.000	-32.000	-10.750	-13.750	-94.750	104.000	1.6250	87.781250
127	156.000	-14.250	7.000	-32.000	-17.000	-58.000	-35.250	20.500	0.3203	3.293203
128	133.000	-23.000	-6.750	-11.750	18.250	35.250	93.250	124.500	2.0078	129.001953

Appendix V Torque Values Measured for each granule batch produced from the experiment of 2^7 Factorial design

Run Number (see Appendix III)	Sieved			Non sieved		
	Bowl (Nm)	Paddle (Nm)	Bowl/Paddle (Nm)	Bowl (Nm)	Paddle (Nm)	Bowl/Paddle (Nm)
1	0.224	0.205	0.219	0.227	0.205	0.232
2	0.232	0.227	0.235	0.232	0.227	0.235
3	0.275	0.248	0.267	0.275	0.248	0.267
4	0.243	0.248	0.232	0.243	0.248	0.232
5	0.248	0.224	0.251	0.248	0.224	0.251
6	0.227	0.232	0.216	0.227	0.237	0.216
7	0.227	0.227	0.221	0.221	0.227	0.227
8	0.254	0.251	0.254	0.254	0.251	0.254
9	0.237	0.259	0.216	0.237	0.259	0.216
10	0.194	0.259	0.175	0.194	0.259	0.175
11	0.270	0.251	0.259	0.270	0.251	0.259
12	0.227	0.227	0.194	0.227	0.227	0.227
13	0.270	0.281	0.267	0.270	0.281	0.267
14	0.232	0.216	0.210	0.232	0.216	0.210
15	0.281	0.245	0.275	0.281	0.245	0.275
16	0.189	0.243	0.183	0.189	0.243	0.183
17	0.243	0.259	0.235	0.243	0.259	0.235
18	0.254	0.248	0.254	0.254	0.248	0.254
19	0.259	0.237	0.259	0.259	0.237	0.259
20	0.270	0.254	0.590	0.270	0.254	0.259
21	0.251	0.235	0.240	0.251	0.235	0.240
22	0.248	0.227	0.243	0.248	0.227	0.243
23	0.251	0.213	0.245	0.251	0.213	0.245
24	0.245	0.224	0.237	0.245	0.224	0.237
25	0.240	0.202	0.227	0.251	0.205	0.245
26	0.219	0.205	0.213	0.224	0.205	0.232
27	0.243	0.210	0.232	0.251	0.256	0.270
28	0.224	0.200	0.220	0.224	0.200	0.221
29	0.221	0.208	0.229	0.243	0.216	0.224
30	0.240	0.219	0.232	0.240	0.219	0.232
31	0.224	0.208	0.221	0.237	0.219	0.237
32	0.216	0.197	0.213	0.208	0.213	0.213

Run Number (see Appendix III)	Sieved			Non sieved		
	Bowl (Nm)	Paddle (Nm)	Bowl/Paddle (Nm)	Bowl (Nm)	Paddle (Nm)	Bowl/Paddle (Nm)
33	0.237	0.216	0.229	0.237	0.210	0.224
34	0.235	0.213	0.235	0.235	0.213	0.235
35	0.224	0.213	0.229	0.216	0.186	0.229
36	0.210	0.189	0.205	0.210	0.189	0.205
37	0.245	0.210	0.229	0.232	0.210	0.227
38	0.240	0.216	0.243	0.240	0.216	0.243
39	0.219	0.210	0.221	0.219	0.208	0.221
40	0.227	0.205	0.227	0.227	0.205	0.227
41	0.251	0.240	0.248	0.251	0.240	0.248
42	0.264	0.229	0.251	0.264	0.229	0.251
43	0.256	0.232	0.245	0.256	0.232	0.245
44	0.248	0.224	0.240	0.248	0.224	0.240
45	0.243	0.224	0.243	0.243	0.224	0.243
46	0.245	0.219	0.243	0.245	0.219	0.243
47	0.262	0.221	0.243	0.262	0.221	0.243
48	0.254	0.243	0.248	0.254	0.243	0.248
49	0.272	0.275	0.262	0.272	0.275	0.262
50	0.202	0.270	0.183	0.202	0.270	0.183
51	0.270	0.254	0.272	0.270	0.254	0.272
52	0.210	0.216	0.175	0.210	0.216	0.175
53	0.262	0.267	0.243	0.262	0.267	0.243
54	0.229	0.264	0.183	0.229	0.264	0.183
55	0.243	0.281	0.286	0.283	0.281	0.286
56	0.243	0.251	0.232	0.243	0.251	0.232
57	0.302	0.259	0.305	0.302	0.259	0.305
58	0.267	0.267	0.254	0.267	0.267	0.254
59	0.275	0.219	0.281	0.275	0.245	0.281
60	0.245	0.219	0.235	0.248	0.219	0.235
61	0.254	0.229	0.254	0.254	0.229	0.254
62	0.251	0.221	0.245	0.251	0.221	0.245
63	0.286	0.262	0.286	0.286	0.262	0.286
64	0.254	0.275	0.235	0.254	0.275	0.235

Run Number (see Appendix III)	Sieved			Non sieved		
	Bowl (Nm)	Paddle (Nm)	Bowl/Paddle (Nm)	Bowl (Nm)	Paddle (Nm)	Bowl/Paddle (Nm)
65	0.237	0.200	0.235	0.243	0.216	0.240
66	0.237	0.205	0.235	0.237	0.205	0.235
67	0.275	0.237	0.275	0.275	0.237	0.275
68	0.270	0.248	0.264	0.270	0.248	0.264
69	0.245	0.219	0.243	0.254	0.224	0.248
70	0.256	0.221	0.243	0.256	0.221	0.243
71	0.281	0.243	0.275	0.281	0.243	0.275
72	0.262	0.267	0.270	0.262	0.267	0.270
73	0.281	0.267	0.281	0.281	0.267	0.281
74	0.248	0.251	0.229	0.248	0.251	0.229
75	0.254	0.248	0.254	0.254	0.248	0.254
76	0.251	0.245	0.243	0.251	0.245	0.243
77	0.281	0.254	0.275	0.281	0.254	0.275
78	0.248	0.245	0.251	0.248	0.245	0.251
79	0.299	0.289	0.291	0.299	0.289	0.291
80	0.259	0.243	0.227	0.259	0.243	0.227
81	0.264	0.227	0.251	0.264	0.227	0.251
82	0.262	0.227	0.240	0.262	0.227	0.240
83	0.245	0.216	0.243	0.245	0.216	0.243
84	0.251	0.237	0.240	0.251	0.237	0.240
85	0.251	0.221	0.243	0.251	0.221	0.243
86	0.237	0.221	0.248	0.237	0.221	0.248
87	0.251	0.229	0.245	0.251	0.229	0.245
88	0.256	0.232	0.248	0.256	0.232	0.248
89	0.232	0.202	0.219	0.243	0.259	0.235
90	0.221	0.205	0.229	0.237	0.200	0.224
91	0.256	0.205	0.227	0.272	-	0.232
92	0.229	0.200	0.224	0.229	0.200	0.224
93	-	-	-	0.243	0.227	0.256
94	0.235	0.205	0.216	0.221	0.208	0.221
95	0.221	0.200	0.216	0.232	-	0.221
96	0.229	0.205	0.235	0.229	0.205	0.237

Run Number (see Appendix III)	Sieved			Non sieved		
	Bowl (Nm)	Paddle (Nm)	Bowl/Paddle (Nm)	Bowl (Nm)	Paddle (Nm)	Bowl/Paddle (Nm)
97	-	-	-	-	-	-
98	0.219	0.200	0.219	0.221	0.210	0.224
99	-	-	-	-	-	-
100	0.221	0.189	0.216	0.205	0.200	0.210
101	0.227	0.200	0.221	-	-	-
102	0.208	0.189	0.202	0.208	0.192	0.210
103	0.237	0.205	0.227	0.237	0.208	0.229
104	0.216	0.200	0.216	0.216	0.229	0.216
105	0.248	0.227	0.245	0.248	0.227	0.245
106	0.243	0.213	0.243	0.243	0.213	0.243
107	0.262	0.227	0.254	0.262	0.227	0.254
108	0.272	0.229	0.259	0.272	0.229	0.259
109	0.237	0.221	0.240	0.237	0.221	0.243
110	0.251	0.221	0.245	0.251	0.221	0.245
111	0.245	0.232	0.240	0.254	0.221	0.245
112	0.259	0.227	0.240	0.259	0.227	0.240
113	0.264	0.221	0.259	0.264	0.221	0.259
114	0.256	0.221	0.254	0.256	0.221	0.254
115	0.272	0.259	0.270	0.272	0.259	0.270
116	0.267	0.243	0.259	0.267	0.243	0.259
117	0.270	0.240	0.259	0.264	0.235	0.254
118	0.254	0.232	0.254	0.254	0.232	0.254
119	0.267	0.259	0.275	0.267	0.259	0.275
120	0.254	0.251	0.248	0.254	0.251	0.248
121	0.235	0.202	0.237	0.229	0.213	0.232
122	0.229	0.202	0.227	0.283	0.256	0.270
123	0.256	0.227	0.245	0.275	0.264	0.270
124	0.254	0.232	0.264	0.254	0.232	0.264
125	0.270	0.227	0.256	-	-	-
126	0.254	0.232	0.254	0.254	0.232	0.254
127	0.245	0.229	0.248	0.248	0.227	0.251
128	0.224	0.208	0.232	0.224	0.208	0.232

Appendix VI Table of spray characteristics with rank order values for each of the eight granule batches prepared from a specific spray variable combination

Run No.	$\bar{x}$	W	SPRAY RATE ml min^{-1}	VARIABLE FORMAT Spray 1	2	3	4	7	6	5	RANK ORDER OF GRANULE BATCHES								MEAN RANK ORDER
								−	−	−	+	−	−	+	+	−	+	+	+	
								−	−	+	−	+	−	+	+	−	+	+	+	
								−	−	−	+	−	+	+	+	−	+	+	+	
29	45	1.8	48.0	−	+	−	−				19	4	13	18	12	28	2	9	13
33	44	1.9	41.5	+	+	−	−				50	65	38	46	61	56	44	49	51
35	39	1.8	41.5	+	+	−	+				64	80	52	79	73	70	43	92	69
31	34	1.9	51.0	−	+	−	+				27	25	6	16	26	14	1	24	17
21	28	1.8	8.5	−	−	−	−				31	39	53	30	112	83	59	118	66
34	27	1.6	64.0	+	+	+	−				78	71	47	68	55	72	67	90	68.5
23	26	1.9	10.75	−	−	−	+				42	66	105	77	117	81	54	111	82
25	24	2.0	6.75	+	−	−	−				101	110	98	99	104	113	126	127	110
27	23	2.0	8.25	+	−	−	+				107	120	119	85	121	125	122	128	116
30	22	1.8	70.25	−	+	+	−				8	22	3	15	17	86	33	32	27
36	22	1.7	64.0	+	+	+	+				69	63	58	75	87	82	45	51	66
32	20	1.8	73.0	−	+	+	+				5	34	4	11	10	23	7	20	14
26	16	2.4	17.5	+	−	+	−				62	93	89	100	102	106	116	124	99
22	15	2.1	17.0	−	−	+	−				21	36	88	29	57	76	40	108	57
28	15	2.4	16.0	+	−	+	+				84	96	94	95	115	97	109	123	102
24	14	2.3	19.0	−	−	+	+				35	48	37	60	91	103	74	114	70

(For definitions of variables see Table 3.5.)

APPENDIX VII Calculations to derive the area available per sodium lauryl sulphate molecule at the surface of atomised solutions

(i) Calculation of the surface area of the atomised solution

Each set of Malvern droplet size distribution data was handled identically. For each of the 11 size ranges a mean radius was calculated and the volume of an average droplet for each size fraction was obtained from the appropriate mean radius. The number of droplets within each size fraction was then derived from the Malvern data of the percentage by weight for each fraction; 100 percent weight was equivalenced to 100ml of granulating solution. The total surface area per 100 ml of granulating solution was then calculated. A typical example of such a calculation is shown in Table VIIa. The total surface area of 100ml of each of the other sprays is listed in Table 5.3.

(ii) Calculation of the number of molecules of SLS in 100 ml of solution

By using the calculated surface areas of the atomised SLS/PVP granulating solution it was possible to calculate the area available by each molecule of SLS at the air/liquid interface of the droplets. This was achieved by initially calculating the number of molecules of SLS in 100 ml in each of the various concentrations of surfactant solution. This was achieved by converting the concentration of SLS to molarity and multiplying it by Avogadros number to give molecules per litre and then dividing by 10. These are listed in Table VIIb.

Table VIIa Typical Calculation of Surface Area generated per 100 ml of solution using the malvern Data for each spray.

This example: 5% PVP, 0% SLS in water through nozzle combination 11 at 1.67 bar air pressure and 1.4 bar liquid pressure.

Droplet Diameter Range (μm)	Mean Droplet Radius (μm)	% wt (from Malvern print out)	Calculated No. of Droplets	Total Surface area per size range (m^2)
5.71 - 7.14	3.2	1.11	8.2×10^9	1.06
7.14 - 9.14	4.1	1.89	6.7×10^9	1.39
9.14 - 11.43	5.1	2.61	4.6×10^9	1.52
11.43 - 14.57	6.5	4.26	3.7×10^9	1.96
14.57 - 18.57	8.3	6.35	2.7×10^9	1.61
18.57 - 23.71	10.6	9.23	1.9×10^9	2.62
23.71 - 30.29	13.5	12.59	1.2×10^9	2.80
30.29 - 38.86	17.3	16.00	7.4×10^8	2.78
38.86 - 50.29	22.3	17.81	3.8×10^8	2.40
50.29 - 64.57	28.7	14.55	1.5×10^8	1.52
64.57 - 84.29	37.2	8.72	4.0×10^7	0.70

Total surface area generated per 100 ml surfactant solution = 20.6 m^2

(iii) Calculation of the number of molecules per square metre at the CMC for sodium lauryl sulphate

The area occupied per surfactant molecule at the critical micelle concentration can be calculated from the use of the Gibbs Free Energy equation. This can be written as,

$$\Gamma = -\frac{C}{RT}\frac{d\gamma}{dc} \qquad \text{Eq. VII.1}$$

where Γ is defined as the surface excess (mol/m^2), C is the overall concentration (mol/dm^3), R is the gas constant, T is the absolute temperature and $\frac{d\gamma}{dc}$ is the slope of the surface tension/concentration curve at concentration C in $Nm^{-1}(mol\ dm^3)^{-1}$.

The surface tension of various concentrations of SLS in a 5% $^w/_v$ PVP solution was measured using a DuNuoy tensiometer. The details of the apparatus and the technique is well documented and gives a direct read out of surface tension (see section 2.3.1). The results are presented in Fig. VII.1.

From these measurements the CMC was found together with the slope of $\frac{d\gamma}{dc}$ and this enabled the number of surfactant molecules per square metre to be calculated by initially calculating the surface excess.

$$= \frac{-\frac{1}{288}}{8.314 \times 293} - \frac{(19 \times 10^{-3})}{(3.47 \times 10^{-3})}$$

Surface excess = 7.78×10^{-6} mol/m^2

From this value the number of excess molecules per square metre was calculated. For the purposes of this calculation this will be taken to be equal to the surface concentration

$$\Gamma \times \text{Avogadros Number}$$

$$= 7.78 \times 10^{-6} \times 6.023 \times 10^{23}$$

i.e. there are 4.7×10^{18} excess molecules per square metre and each molecule occupies the reciprocal of this number, i.e. 2.13×10^{-19} m^2.

Thus at the CMC there are 4.7×10^{18} molecules per square metre with each molecule occupying 2.13×10^{-19} square metres.

Table VIIb Calculation of the number of molecules of sodium lauryl sulphate in various concentrations of solution.

Concentration Sodium Lauryl Sulphate (%w/v)	Conversion to Molarity $\frac{g/l}{\text{Molec. Wt. of SLS}}$	Molarity	Number of Molecules in 100 ml solution
(CMC 0.1	$\frac{1}{288}$	3.47×10^{-3}	2.09×10^{20})
0.5	$\frac{5}{288}$	1.74×10^{-2}	1.05×10^{21}
1.0	$\frac{10}{288}$	3.47×10^{-2}	2.09×10^{21}
2.5	$\frac{25}{288}$	8.68×10^{-2}	5.24×10^{21}
5.0	$\frac{50}{288}$	1.74×10^{-1}	1.04×10^{22}
7.5	$\frac{75}{288}$	2.60×10^{-1}	1.57×10^{22}

(iv) Calculation of the area available for each surfactant molecule at the air/liquid interface of an atomised solution

The area available for each surfactant molecule at the air/liquid interface of each of the sprays was then calculated. As in the previous section, the surface excess concentration was calculated from the Gibbs Free Energy equation. Data generated from these calculations are given in Table VIIc.

The area available per molecule was calculated by dividing the surface area of the spray (from Table 5.3) by the surface excess concentration (from Table VIIb).

Table VIIc Area available for each sodium lauryl sulphate molecule at the air/liquid interface of the atomised spray solution.

Concentration Sodium Lauryl Sulphate (% w/v)	m^2/number of molecules	Area (m^2) occupied per molecule
CMC	-	2.13×10^{-19}
0.5	$23.4/1.05 \times 10^{21}$	2.23×10^{-20}
1.0	$25/2.09 \times 10^{21}$	1.20×10^{-20}
2.5	$26.75/5.23 \times 10^{21}$	5.11×10^{-21}
5.0	$26.75/1.05 \times 10^{22}$	2.55×10^{-21}
7.5	$25/1.57 \times 10^{22}$	1.59×10^{-21}

Therefore in all cases the area available per molecule is less than that occupied by one molecule of SLS at the CMC, in 5% aqueous PVP.

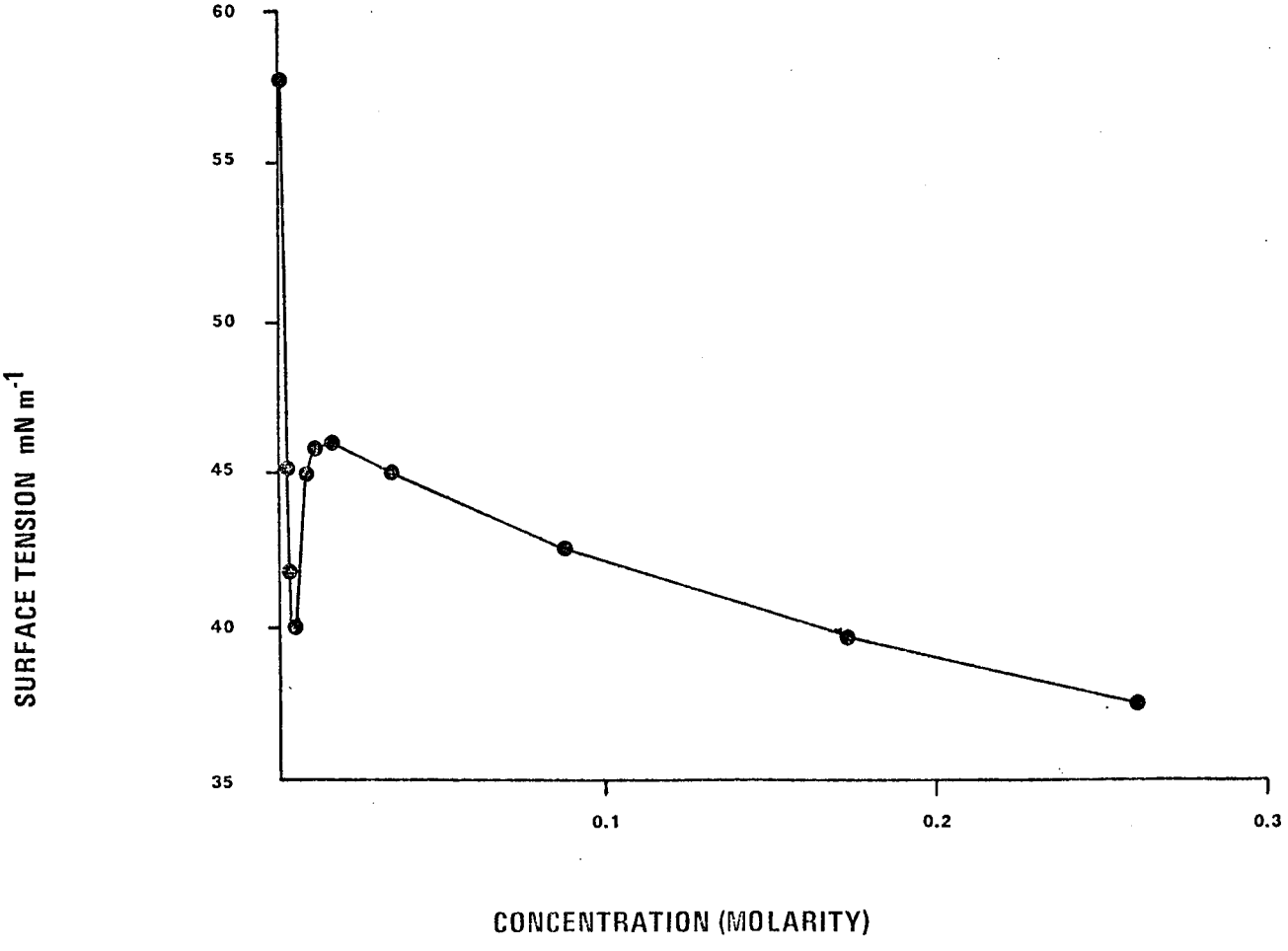


Fig. VII.1 Surface Tension-Concentration curve for Sodium Lauryl Sulphate dissolved in 5% w/v PVP Solution

Appendix VI I Published Work in Fluidised Bed Granulation Technology and Related Fields, in which M. Banks was involved during the course of this study

1. The wettability of powders during fluidised bed granulation.
   M.E. Aulton, M. Banks and D.K. Smith.
   Presented by M. Banks to the British Pharmaceutical Conference, Sheffield, September, 1976.
   Published:
   J. Pharm Pharmac., 29, Suppl., 59P, 1977.

2. A fluorescent technique for the observation of polyvinylpyrrolidone binder distribution in granules.
   M.E. Aulton, M. Banks and I. ab I. Davies.
   Presented by M. Banks to the British Pharmaceutical Technology Conference, London, July, 1978.
   Published:
   Drug Dev. and Ind. Pharm., 4 (6), 537-539, (1978).

3. The factors affecting fluidised bed granulation.
   M.E. Aulton and M. Banks.
   Mfg. Chem. and Aerosol News, 49 (12), 50 - 56 (1978).

4. Influence of the hydrophobicity of the powder mix on fluid bed granulation.
   M.E. Aulton and M. Banks.
   Presented at the 2nd International Conference on Powder Technology in Pharmacy held in Basle, Switzerland, June 1979 and published in the proceedings of this conference.(Powder Advisory Centre, London).

5. The measurement of spray droplet size distribution.
   M.E. Aulton and M. Banks.
   A scientific demonstration presented to the British Pharmaceutical Conference, Exeter, September, 1979.
   Published:
   J. Pharm. Pharmac., 31, Suppl., 102P, (1979).